Trends

Assessing consistent and meaningful trends is essential when interpreting any large study with multiple endpoints, clinical areas, and covariates. However, caution must be used when assessing trends. Increased numbers of abnormalities or means with increased dioxin levels across medically related variables within a clinical area might indicate a dioxin effect. In this case, it is important to note that there is a moderate-to-strong correlation between some endpoints. Hence, the strength of the trends also must be considered when assessing the suspected association.

Power Limitations

The fixed size of the Ranch Hand cohort limits the ability of this study to detect a dioxin association. This limitation is most obvious concerning specific types of cancer, such as soft tissue sarcoma and non-Hodgkin's lymphoma, which are so uncommon that fewer than two cases are expected in this study, indicating that this study has virtually no statistical power to detect low-to-moderate associations (relative risks less than 5) with dioxin. On the other hand, these sample sizes are sufficient to detect very small mean shifts in the continuously distributed variables (see Chapter 4). For example, with regard to IgG, this study has approximately 90 percent power to detect a mean shift of 1 percent. The detection of significant mean shifts without a corresponding indication of increased Ranch Hand abnormalities or disease is considered to be of little importance or it may be an artifact of multiple testing. This study has good power to detect relative risks of 2.0 or more with respect to diseases, such as heart disease and basal cell carcinoma, occurring at prevalences of at least 5 percent in unexposed populations.

In an attempt to overcome the lack of power to detect group differences for specific types of systemic cancer, all types of systemic cancer were combined into a single variable. It is still possible, however, that an increased risk could exist for a particularly rare type of cancer, allowing that increased risk to be missed in this study.

Strength of Association

Ideally, an adverse effect, if it exists, would be revealed by a strong association between categorized current dioxin and a disease condition; that is, by a statistically significant relative risk greater than 2.0 for Ranch Hands in the high current dioxin category relative to the unexposed Comparisons (5). Statistically significant relative risks less than 2.0 are considered to be less important than larger risks because the relative risks less than 2.0 can easily arise due to unperceived bias or confounding. Relative risks greater than 5.0 are less subject to this concern. The numbers 2 and 5 are rules of thumb regarding analyses of association between a dichotomous endpoint (disease, no disease) and dichotomized exposure (exposed, unexposed). No such rules have been published regarding the analysis of continuously distributed endpoints (such as cholesterol) versus continuously distributed exposure (such as initial or current dioxin in models 1 and 2).

Biological Credibility

The assessment of biological credibility requires consideration of the following question. In biological terms, can it be understood how the exposure under study could produce the effect of interest? While a lack of biological credibility or even a contradiction of biological knowledge can lead to the dismissal of a significant result, the failure to perceive a mechanism may reflect only ignorance of the state of nature. On the other hand, it is easy to ascribe biological mechanisms that relate almost any exposure to almost any cancer. Thus, while pertinent, the response to this question is not always convincing.

Interpretation of Negative Results

A 1985 study (6) presents minimal sample-size criteria for proof of safety and hazard in studies of environmental and occupational exposures. The study was directed at rectifying widespread misconceptions about proof of safety in the medical and scientific establishments and in other groups involved in public health and safety. Thus, a lack of significant results relating dioxin to a particular disease only means that this study is unable to detect a relationship between dioxin and health. This does not imply that a relationship does not exist, but that, if it does exist, it was not detected. A lack of significant results does not mean that dioxin is safe or that there is no relationship between dioxin and health, because this study is not designed, nor was it intended, to establish safety. This study was designed to determine whether a hazard existed for the exposed personnel and not whether dioxin was "safe."

Interpretation of the Coefficient of Determination

The coefficient of determination, R^2, measures the proportionate reduction of the total variation in a continuously distributed health variable y associated with the set of independent variables in a linear regression. A large value of R^2 does not necessarily imply that the fitted model is a useful one. Large values of R^2 would occur, for example, if y is regressed on an independent variable with only two observed values. On the other hand, very small values of R^2 are generally seen in observational studies because little or no control has been applied in the assignment of the values of the "treatment" (initial or current dioxin) or the conditions under which the "treatment" has been applied. In this study, the dioxin measurements were taken many years after exposure and are themselves subject to measurement error. Thus, in most analyses, the values of R^2 in this study are small.

Clinical Interpretation of Discrete versus Continuous Data

Small but significant mean differences in a continuously measured health variable (e.g., systolic blood pressure) between exposed and unexposed groups when there are no corresponding differences in the percentage of abnormal tests are difficult to assess in any study. In this study, significant mean differences are sometimes observed without a corresponding group difference in the proportion outside the normal range. Such contrasting situations may be interpreted as spurious outcomes of no clinical consequence, or as a subclinical dioxin effect. Significant trends in the mean with increasing levels of dioxin are interpreted as a dioxin-related effect if a corresponding trend is seen in the proportion above or below the normal range.

Minimal versus Maximal Results

The minimal and maximal assumptions for Ranch Hands having background dioxin levels (≤10 ppt) were imposed to address the unknown exposure history of this subgroup. There were 345 Ranch Hands in this "unknown" category. In the minimal analyses, all of these were excluded from the data set. In the maximal analyses, only those with less than or equal to 5 ppt (n=124) were excluded. The intent of these two analyses was to "trap" the true dioxin versus health relationship between them. The results of the maximal analyses appear to be statistically significant more often than those of the minimal analyses. This could be due to the larger sample size of the maximal cohort or it could be due to the uncertainty of true exposure in Ranch Hands between 5 ppt and 10 ppt. There are no additional data available at this time with which to resolve these two interpretations.

Graphics

The histograms, scatter plots, and graphical descriptions of interactions were included as aids to interpretation. The graphics alone are not sufficient to assess the relationship between dioxin and health. For example, a trend may be seen in a plot, but it could be statistically nonsignificant because the number of abnormalities is small. On the other hand, a statistically significant result can be clarified by the graphics, especially if the result depends on a few data points that appear far from the main cluster. Such points are termed "outliers" by statisticians. Outside of the initial quality control review activities, no additional effort was made to identify statistically significant outliers in this report.

The Checkmark Pattern

In many model 3 analyses, the "unknown" Ranch Hand group has the lowest percentage of abnormalities; this phenomenon is termed "the checkmark pattern." These patterns are interesting but are without explanation at this time. Some reanalyses were accomplished with adjustment for military rank (officers, enlisted personnel), but the checkmark pattern remained after adjustment. This effect will be a subject of continued focus in future reports.

Extrapolation to Army Ground Troops

Extrapolation of the serum dioxin results to the general population of ground troops who served in Vietnam is difficult because Ranch Hand and ground troop exposure situations were quite different. Based on serum dioxin testing results done by CDC (7) and others (8), nearly all ground troops tested have current levels of dioxin similar to background levels. Even ground troops who served in herbicide-sprayed areas of Vietnam had current levels indistinguishable from levels in men who never left the United States (with means of 4.2 ppt and 4.1 ppt, respectively). The AFHS subgroup most like the ground troops in terms of current dioxin levels are Ranch Hands who currently have background levels of dioxin (10 ppt or less—designated as the "unknown" current dioxin category in the model 3 analyses). Therefore, if the results of the AFHS are applied to the general population of Vietnam veterans, the focus should be on the unknown Ranch Hand versus background Comparison contrast in the model 3 analyses. However, extrapolating the results of these analyses to Vietnam veterans should still be made cautiously. There may be demographic distinctions between the unknown group of Ranch Hands and other Vietnam veterans that may be related to health. Also, if Ranch Hands in the unknown current dioxin category showed a significant health detriment relative to Comparisons in the background category, but there was no significant detriment for Ranch Hands in the high current dioxin category, the biological plausibility of such an effect would be questionable because this would not indicate a dose-response effect. In general, the adjusted model 3 analyses found that Ranch Hands in the unknown current dioxin category did not show a significant health detriment relative to Comparisons in the background current dioxin category. This was particularly true for the variables that exhibited a significant high versus background contrast.

Summary of Results

Many readers of this report will attempt to tally statistically significant results across clinical areas and study cycles. A study of this scope with a multitude of endpoints and no prescribed strength of association to declare an effect demands, and at the same time defies, meaningful summary tabulation. Such summaries can be misleading because they ignore correlations between the endpoints, correlations between study-cycle results, and the nonquantifiable medical importance of each endpoint. In fact, many endpoints are redundant (e.g., psychological scales and indices developed from combining multiple variables) so as not to miss a dioxin effect and some (such as those arising from measures of pulmonary function) were not suspected beforehand to be related to dioxin exposure.

In addition, such tabulations combine endpoints that medically are not comparable. For example, a diminished sense of smell is of less medical importance than the presence of malignant neoplasm. Statisticians have attempted to summarize multidimensional repeated measures data with growth curve analyses. Such methods were not used in this study because they apply to continuously distributed data only, do not account for medical importance, and reduce the data too much.

Nevertheless, given the lack of adequate summary statistics, the tally of significant results will occur. Such summaries can be misleading and must be interpreted carefully.

CONCLUSION

The interpretation of the AFHS requires careful consideration of potential biases, interactions, consistency of results, the multiple-testing artifact, dose-response patterns, trends, power limitations, strength of association, and biological credibility.

CHAPTER 1

REFERENCES

1. Thomas, W.F., W.D. Grubbs, T.G. Karrison, M.B. Lustik, R.H. Roegner, D.E. Williams, W.H. Wolfe, J.E. Michalek, J.C. Miner, and R.W. Ogershok. 1990. Epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: 1987 followup examination results, NTIS: AD A 222 573. USAF School of Aerospace Medicine, Human Systems Division, Brooks Air Force Base, Texas.

2. Pirkle, J.L., W.H. Wolfe, D.G. Patterson, L.L. Needham, J.E. Michalek, J.C. Miner, M.R. Peterson, and D.L. Phillips. 1989. Estimates of the half life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Vietnam veterans of Operation Ranch Hand. *J. of Toxicol. and Environ. Health* 27:165-71.

3. Mocharelli, P., D.G. Patterson, Jr., A. Marochi, and L.L. Needham. 1990. Pilot study (Phase II) for determining polychlorinated dibenzo-p-dioxin (PCDD) and polychlorinated dibenzofuran (PCDF) levels in serum of Seveso, Italy, residents collected at the time of exposure: Future plans. *Chemosphere* 20:967-74.

4. Rosenbaum, P.R. 1984. The consequences of adjustment for a concomitant variable that has been affected by the treatment. *Journal of the Royal Statistical Society* 147:656-66.

5. Breslow, N.E., and N.E. Day. 1980. *Statistical methods in cancer research.* Lyon, France: International Agency for Research on Cancer.

6. Bross, I.D. 1985. Proof of safety is much more difficult than proof of hazard. *Biometrics* 41:785-93.

7. The Centers for Disease Control. 1988. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in U.S. Army Vietnam-era veterans. *JAMA* 260:1249-54.

8. Kahn, P.C., M. Gochfeld, M. Nygren, M. Hansson, C. Rappe, H. Velez, T. Ghent-Guenther, and W.P. Wilson. 1988. Dioxins and dibenzofurans in blood and adipose tissue of Agent Orange-exposed Vietnam veterans and matched controls. *JAMA* 259:1661-67.

CHAPTER 2

DIOXIN ASSAY

SAMPLE ACQUISITION

Blood for the serum dioxin assay was drawn on the morning of the second day of the physical examination in 1987. Participants who volunteered to give blood for the dioxin assay fasted after midnight (water was allowed). Blood was drawn from the participants with a 15-gauge needle into a blood pack unit without anticoagulant. The blood pack units had been tested previously by the Centers for Disease Control (CDC) and were found to be free of dioxin contamination. Participants selected for the immunology studies had 250 ml of blood drawn; all others had 350 ml of blood drawn. After drawing, the bags were clamped, labeled, placed upright at room temperature, and allowed to clot for 7 hours. Appendix B-1 contains the Scripps Clinic and Research Foundation's (SCRF) procedure for the dioxin blood collection and processing.

The unit bags were centrifuged for 15 minutes at 4500 RPM at a temperature of 4°C to 10°C. The serum was then transferred to transfer packs (also dioxin-free) from the spun unit bag by a plasma extractor. The transfer packs were spun for 15 minutes at 4500 RPM. The serum was then placed into four Wheaton bottles: two 4-ounce bottles for the serum dioxin analysis, a 5 ml bottle for the lipid profile, and a 10 ml bottle for reserve serum. Samples were logged and stored at -20°C or less until shipment. Frozen samples, packed in dry ice in styrofoam boxes, were shipped twice weekly from SCRF, La Jolla, California, to Brooks Air Force Base, Texas. At Brooks Air Force Base, inventory was taken and the specimens were stored at -70°C until shipment to the CDC. All samples were coded so that the CDC was blinded to the group status (Ranch Hand, Comparison) of each specimen.

ANALYTICAL METHOD

The serum samples were analyzed for dioxin in analytical runs that consisted of a method blank, three unknown samples, and a quality control pool sample (1, 2). Cholesterol esters, triglycerides, and high-density lipoprotein cholesterol were determined in duplicate by standard methods. Total phospholipids were determined in duplicate by modifying (3) the Folch et al. procedure (4). Fresh cholesterol was determined in duplicate by an enzymatic method (5). For each analysis, the results of the duplicate analyses were averaged and the mean was used. These results were used to calculate the concentrations of (a) total lipids using the summation method (6), (b) low-density lipoprotein cholesterol, and (c) very low-density lipoprotein cholesterol (7).

QUALITY CONTROL

Quality assurance was maintained with matrix-based materials that are well characterized for dioxin concentration and isotope ratios to ensure that the analytical system was in control. Quality control (QC) charts were maintained for each of these materials (five serum pools). The concentration in the QC sample from each analytical run must be within 99 percent confidence limits established for the QC material (8, 9). The unlabeled and carbon-13 labeled internal standard isotope ratios must be within 95 percent confidence limits. All analytical runs for the dioxin and lipid measurements were in control. No dioxin was detected

TABLE 2-1.

Report Field Definition

Report Field Value	Definition
G	Good result
GML	Good result, missing lipids
GND	Good result, below limit of detection
GNQ	Good result, below limit of quantitation
NR	No result

in the blanks (on-column injection of 100 femtograms from a standard solution produces detectable signals that are greater than three times the background noise).

DATA DELIVERED TO THE AIR FORCE BY THE CENTERS FOR DISEASE CONTROL

The dioxin data used in this report were derived from a data base of results on 932 Ranch Hands and 888 Comparisons delivered by the CDC in January 1990. The CDC sent data on whole-weight and lipid-weight dioxin concentrations to the Air Force together with the total sample weight, weights of lipid fractions, total lipid weight, the detection limit, quantitation limit, and all associated QC information, including results from blank samples. Table 2-1 defines a "report" field in the data base.

Some participants (150 Ranch Hands and 50 Comparisons) participated in a pilot dioxin study in April 1987 (8). Four of these (three Ranch Hands and one Comparison) had a missing dioxin result (report=NR), the rest had good results (report=G). The remaining 147 Ranch Hands and 49 Comparisons were included in the dioxin data base from which the analysis data set for this report was derived. Of these, 145 Ranch Hands and 48 Comparisons were also fully compliant to the 1987 physical examination. Forty-seven of the pilot study participants (43 Ranch Hands and 4 Comparisons) also had blood drawn for the dioxin assay at the 1987 physical examination (May 1987 through March 1988). If a participant was assayed during the pilot study but not at the 1987 physical examination, or if he was assayed at the pilot study and at the 1987 physical examination, then his pilot study assay was used.

Table 2-2 shows counts of study participants by group, report, and compliance to the 1987 physical examination.

TABLE 2-2.

Sample Sizes by Group, Report, and Compliance to the 1987 Physical Examination

	Ranch Hand		Comparison	
Report	Fully Compliant	Noncompliant	Fully Compliant	Noncompliant
G	858	2	761	1
GML	0	0	1	0
GND	8	0	43	0
GNQ	20	0	51	0
NR	44	0	31	0
Total	930	2	887	1

Missing dioxin results (report=NR or GML) and nonquantitatable dioxin results (report=GNQ) were excluded from analysis in this report. The resulting effective sample sizes (866 Ranch Hands and 804 Comparisons) were determined by the condition that the participants were fully compliant to the 1987 physical examination. Table 2-3 summarizes this sample size reduction.

TABLE 2-3.

Sample Sizes Used in This Report

		Ranch Hand	Comparison
Fully compliant to 1987 physical examination and assayed for dioxin		930	887
	Report		
Less	GNQ	(20)	(51)
	NR	(44)	(31)
	GML	(0)	(1)
Total		866	804

TABLE 2-4.

Dioxin Result Summary of 866 Ranch Hands and 804 Comparisons

	Ranch Hands			Comparisons		
Stratum	n	Median	Range	n	Median	Range
Officer	319	7.8	0-42.6	291	4.7	0-18.5
Enlisted Flyer	148	18.1	0-195.5	127	4.0	0-12.8
Enlisted Groundcrew	399	24.0	0-617.8	386	4.0	0-54.8
Total	866	12.8	0-617.8	804	4.2	0-54.8

Table 2-4 summarizes, by military occupation and group, the dioxin results among the 866 Ranch Hands and 804 Comparisons whose results were used in analyses of dioxin versus health in this report.

The 95th, 98th, and 99th percentiles of the Ranch Hand dioxin distribution were 110.8, 168.0, and 211.0 ppt; the corresponding Comparison percentiles were 8.3, 10.2, and 14.2 ppt.

CDC subsequently provided 314 Comparison dioxin results after January 1990 (the beginning date for statistical analyses involving Comparison data). Of these 314 dioxin results, 253 had a report field value of G or GND, 24 had a report field value of GNQ, and 37 had a report field value of NR (no result). Of the 253 Comparisons, the median current dioxin result was 4.1 ppt, the range of levels was between 0 ppt and 13.6 ppt, and the first and third quartiles were 2.9 ppt and 5.8 ppt. The percentages of the 253 Comparisons and of the 804 Comparisons analyzed in this report, having levels less than 10 ppt, were 97.8 and 97.6, respectively. A statistical contrast of the dioxin distributions of these 253 and the 804 Comparisons included in this report revealed no significant difference ($p=0.15$), as expected.

The phrase "serum dioxin" is used throughout this report and is defined as the serum lipid-weight concentration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Its relationship with dioxin concentrations in other compartments, such as adipose tissue, is a subject of continuing research. The lipid-weight dioxin measurement, also called "current dioxin body burden" in this report, is a derived quantity calculated from the formula $ppt = ppq \cdot 102.6/W$, where ppt is the lipid-weight concentration, ppq is the actual weight of dioxin in the sample in femtograms, 102.6 corrects for the average density of serum, and W is the total lipid weight of the sample (9). The correlation between the serum lipid-weight concentration and adipose tissue lipid-weight concentration of TCDD has been observed to be 0.98 in 50 persons from Missouri (10). Using the same data, Patterson et al. calculated the partitioning ratio of dioxin between adipose tissue and serum on a lipid-weight basis as 1.09 (95% C.I.: [0.97,1.21]). On the basis of these data, a one-to-one partitioning ratio of dioxin between lipids in adipose tissue and the lipids in serum cannot be excluded. Measurements of dioxin in adipose tissue generally have been accepted as representing the body burden concentration of dioxin. The high correlation between serum dioxin levels and adipose tissue dioxin levels in their study suggests that serum dioxin is also a valid measurement of dioxin body burden.

CHAPTER 2

REFERENCES

1. Patterson, D.G., Jr., J.S. Holler, C.R. Lapeza, Jr., L.R. Alexander, D.F. Groce, R.C. O'Conner, S.J. Smith, J.A. Liddle, and L.L. Needham. 1986. High resolution gas chromatographic/high resolution mass spectrometric analysis of human adipose tissue for 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Annals of Chemistry* 58:705-13.

2. Patterson, D.G., Jr., L. Hampton, C.R. Lapeza, Jr., W.T. Belser, V. Green, L.R. Alexander, and L.L. Needham. 1987. High resolution gas chromatographic/high resolution mass spectrometric analysis of human serum on a whole weight and lipid weight basis for 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Annals of Chemistry* 59:2000-05.

3. Beveridge, J., and S. Johnson. 1949. The determination of phosolipid phosphorous. *Canadian Journal* 27E:159-63.

4. Folch, J., M. Lees, and G.H. Sloan-Stanley. 1957. A simple method for the isolation and purification of total lipids from animal tissue. *Journal of Biology and Chemistry* 226:497-509.

5. Cooper, G.R., P.H. Duncan, J.S. Hazelhurst, D.T. Miller, and D.D. Bayse. 1982. Cholesterol, enzymic method. In Vol. 9, *Selected methods for the small clinical chemistry laboratory*, ed. W.E. Faulkner and S. Meites. Washington, DC: American Association for Clinical Chemistry.

6. Cheek, C.S., and D.F. Wease. 1969. A summation technique for serum total lipids: Comparison of methods. *Clinical Chemistry* 15:102-07.

7. Friedewald, W.T., R.I. Levy, and D.S. Fredrickson. 1972. Estimation of the concentration of low density lipoprotein cholesterol in plasma, with use of the preparative centrifuge. *Clinical Chemistry* 18:499-502.

8. Wolfe, W.H., J.E. Michalek, J.C. Miner, and M.R. Petersen. 1988. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in Air Force Health Study participants. Preliminary report. *Morbidity and Mortality Weekly Report* 37:309-11.

9. Akins, J.R., K. Waldrep, and J.T. Bernert, Jr. 1989. The estimation of total serum lipids by a completely enzymatic "summation" method. *Clinica Chimica Acta* 184:219-26.

10. Patterson, D.G., L.L. Needham, J.L. Pirkle, D.W. Roberts, J. Bagby, W.A. Garret, J.S. Andrews, Jr., H. Falk, J.T. Bernert, E.J. Sampson, and V.N. Houk. 1988. Correlation between serum and adipose tissue levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in 50 persons from Missouri. *Archives of Environ. Toxicol.* 17:139-43.

CHAPTER 3

THE RELATIONSHIP BETWEEN THE EXPOSURE INDEX AND DIOXIN BODY BURDENS IN RANCH HANDS

INTRODUCTION

An increased prevalence of adverse health effects at higher levels of exposure represents the classic dose-response relationship sought in any study of environmental or occupational exposure to potentially toxic substances. In previous Air Force Health Study (AFHS) reports, the potential relationship between clinical endpoints and herbicide exposure in Ranch Hands was assessed using a calculated estimate of TCDD exposure, hereafter called the exposure index.

The exposure index was constructed solely from available historical data to measure the potential exposure of a Ranch Hand to any of four 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-containing herbicides: Herbicides Orange, Purple, Pink, and Green (1). The index was only an estimate of exposure, because the actual concentration of TCDD in the herbicides varied with type and lot as well as with individual work habits and duties. The calculation of the index was necessary because actual measures of dioxin exposure on individuals during or just after their Southeast Asia tours were not feasible at that time.

Exposure Index Definition

The exposure index for a Ranch Hand was defined as the product of a TCDD weighting factor and the gallons of TCDD herbicides sprayed during his tour divided by the number of Ranch Hands sharing his duties during his tour. The TCDD weighting factor reflected the estimated relative concentration of TCDD in the herbicides sprayed; these were 2 ppm in Herbicide Orange, 33 ppm in Herbicide Purple, 66 ppm in Herbicide Pink, and 66 ppm in Herbicide Green, as determined from archived samples (1). Based on procurement records and historical spray records, a combination of Herbicides Green, Pink, and Purple was sprayed between January 1962 and June 1965. The estimated mean concentration of TCDD in this combination during that period was 48 ppm. The "Herbs" tape and other data sources (1) indicate that only Herbicide Orange was sprayed by Operation Ranch Hand after 1 July 1965. Normalizing to Herbicide Orange, the weighting factor was defined as 24 for a Ranch Hand with a tour of duty before 1 July 1965 and as 1 for a Ranch Hand with a tour of duty after 1 July 1965.

A table showing gallons of TCDD-containing herbicide sprayed for each month of the Ranch Hand operation was constructed using data derived from the Herbs tape, Contemporary Historical Evaluation and Combat Reports, and quarterly operations reports. Gallons of Herbicides Purple, Pink, and Green were converted to Herbicide Orange equivalents based on the TCDD weighting factor. Appendix B-2 contains this table.

The tour dates and military occupation of each Ranch Hand were verified by review of military records. The study design reduced the many occupational categories (specified by an Air Force Specialty Code) to five: (1) officer-pilot, (2) officer-navigator, (3) officer-nonflying, (4) enlisted flyer, and (5) enlisted groundcrew. After computing the index for each Ranch Hand, he was placed in one of three exposure categories ("low," "medium," and "high")

TABLE 3-1.

Exposure Index Categorization of 866 Fully Compliant Ranch Hands With TCDD Results

Occupation	Exposure Index Category	Effective Herbicide Orange Gallons Corresponding to Exposure Index Category	Number of Ranch Hand Participants in Exposure Index Category
Officer	Low	<35,000	109
	Medium	35,000-70,000	104
	High	>70,000	106
Enlisted Flyer	Low	<50,000	43
	Medium	50,000-85,000	57
	High	>85,000	48
Enlisted Groundcrew	Low	<20,000	127
	Medium	20,000-27,000	139
	High	>27,000	133
Total			866

according to the tertiles of the index in three occupational categories: officer, enlisted flyer, and enlisted groundcrew. The officer category consisted of officers who were pilots, navigators, or nonflyers. Table 3-1 shows counts of the 866 Ranch Hands who subsequently had serum levels determined and who were fully compliant to the 1987 examination according to their assigned exposure index category. Nonflying officers were assigned an exposure index value of zero and were placed in the "low" category of exposure.

The index was not useful for assessing the exposure of any specific individual because it did not account for variation in exposures due to work habits and duties. For example, it was known that some Ranch Hand enlisted ground personnel primarily were occupied with administrative duties and probably had little actual contact with herbicides. Other enlisted Ranch Hands periodically greased an emergency dump valve inside the spray tank. To do this, the Ranch Hand had to enter the spray tank and apply the grease to a valve at the bottom of the tank which contained at least 2 inches of herbicide.

In past reports, every clinical endpoint was evaluated for a dose-response effect versus the calculated exposure index. Few significant trends were found. Those that were found were not consistent with other findings or were medically implausible or both.

The Dioxin Assay

The dioxin assay provides a direct measurement of current dioxin burden which, together with assumptions regarding the decay process, provides an approximate measure of TCDD exposure in Ranch Hands and Comparisons. The assay is preferred over the calculated exposure index, because it is a direct rather than indirect measure of TCDD exposure. Confidence in the assay as a measure of TCDD exposure is heightened by the following: (a) Ranch Hand results are generally greater than those of the Comparisons, and (b) Ranch Hand results are logically placed relative to those of industrially exposed individuals and people exposed to TCDD in Seveso, Italy (2). Additionally, differences in TCDD body burdens between the three occupational groups within the Ranch Hand group are in accordance with recent information regarding the relative exposure of the occupational cohorts gleaned from interviews of two Ranch Hand crew chiefs, administered before any Ranch Hands were assayed for TCDD. Based on those interviews, it appears that Ranch Hand groundcrew had more opportunity for cutaneous exposure than enlisted flyers or officers and that enlisted flyers had more opportunity than officers for cutaneous exposure and inhalation of herbicide spray. These aspects will be investigated during an analysis of a questionnaire administered to all assayed Ranch Hand enlisted ground personnel before they received their serum dioxin assay results. These men were asked whether they entered the spray tank to service the dump valve and if so, how often. Other questions addressed daily exposures reported by crew chiefs during in-person interviews at Brooks Air Force Base, Texas, in 1988.

The relative position of the Ranch Hand results in contrast to other study cohorts lends credence to the assay as a measure of TCDD exposure. The Ranch Hand serum dioxin results are less than those observed in people exposed in Seveso, Italy, and are greater than those observed in U.S. Army ground troops and the Air Force Comparison cohort. Ranch Hand dioxin results are also generally less than those observed in a National Institute for Occupational Safety and Health study of workers who produced trichlorophenol and its derivatives (3).

The Exposure Index versus the Dioxin Assay

The relationship between the assay results and the exposure index provides an indication of the extent to which Ranch Hands have been misclassified by the exposure index. Figure 3-1 shows a scatter plot of the extrapolated initial dioxin concentrations of the 742 Ranch Hands in the maximal cohort (having current dioxin greater than 5 ppt; see Chapter 4, Statistical Methods) versus the continuously distributed exposure index. The extrapolated initial dioxin concentration (I) was computed from the current dioxin level (C) and the time in years between the end of the Vietnam tour and the dioxin blood draw (T) with the formula $I = C \cdot 2^P$, where $P = T/7.1$.

Both distributions are highly skewed, hence the concentration of observations near the origin. Figure 3-2 shows the bivariate scatter plot of the logarithms of these quantities. The logarithms are taken to the base 2 and 1 was added to the exposure index prior to taking the logarithm.

The corresponding scatter plots of current dioxin versus the exposure index and the logarithms of these quantities in all 866 Ranch Hands fully compliant to the 1987 examination

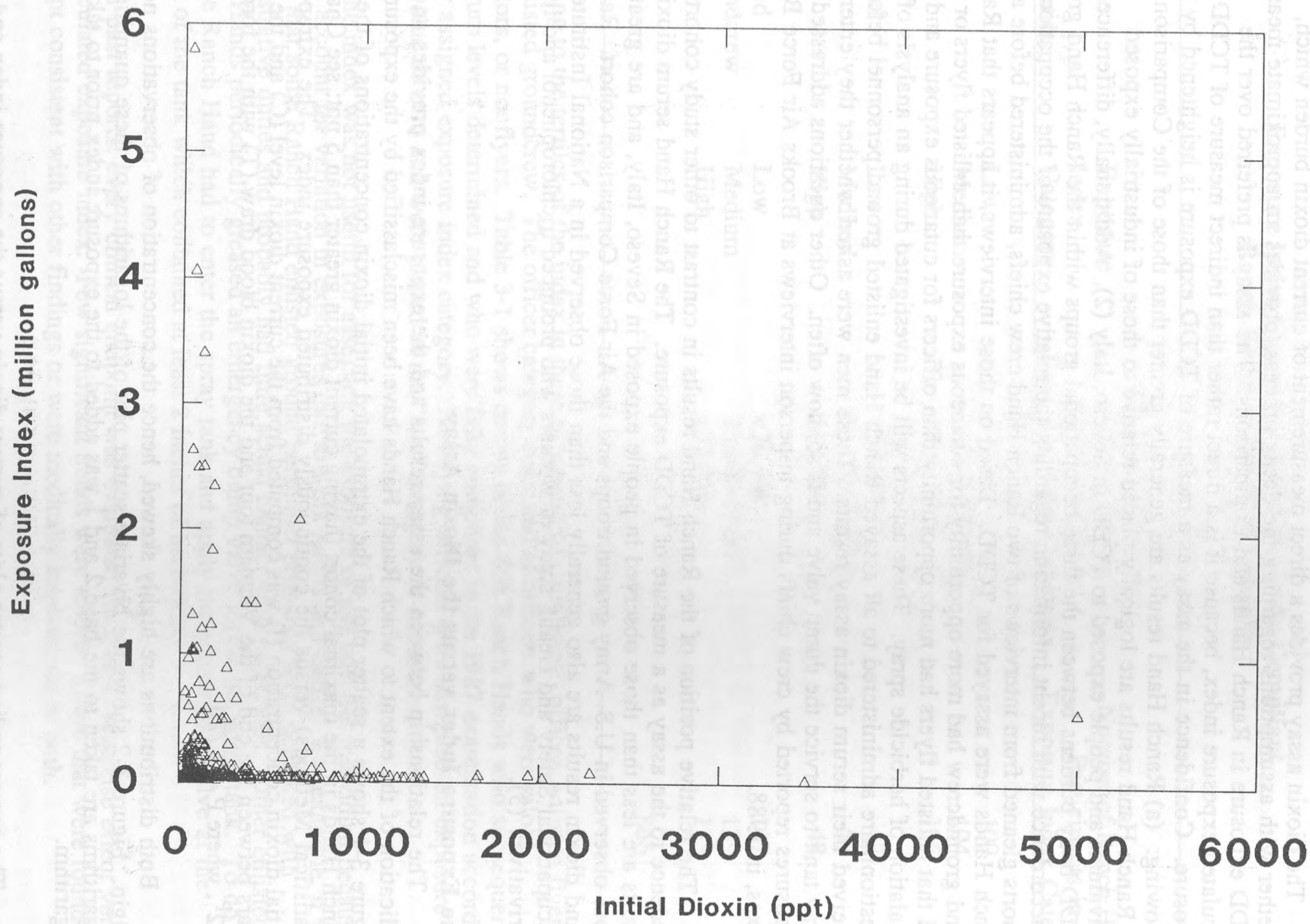

FIGURE 3-1. Initial Dioxin versus the Exposure Index in Ranch Hands With Current Dioxin Greater Than 5 ppt (N=742)

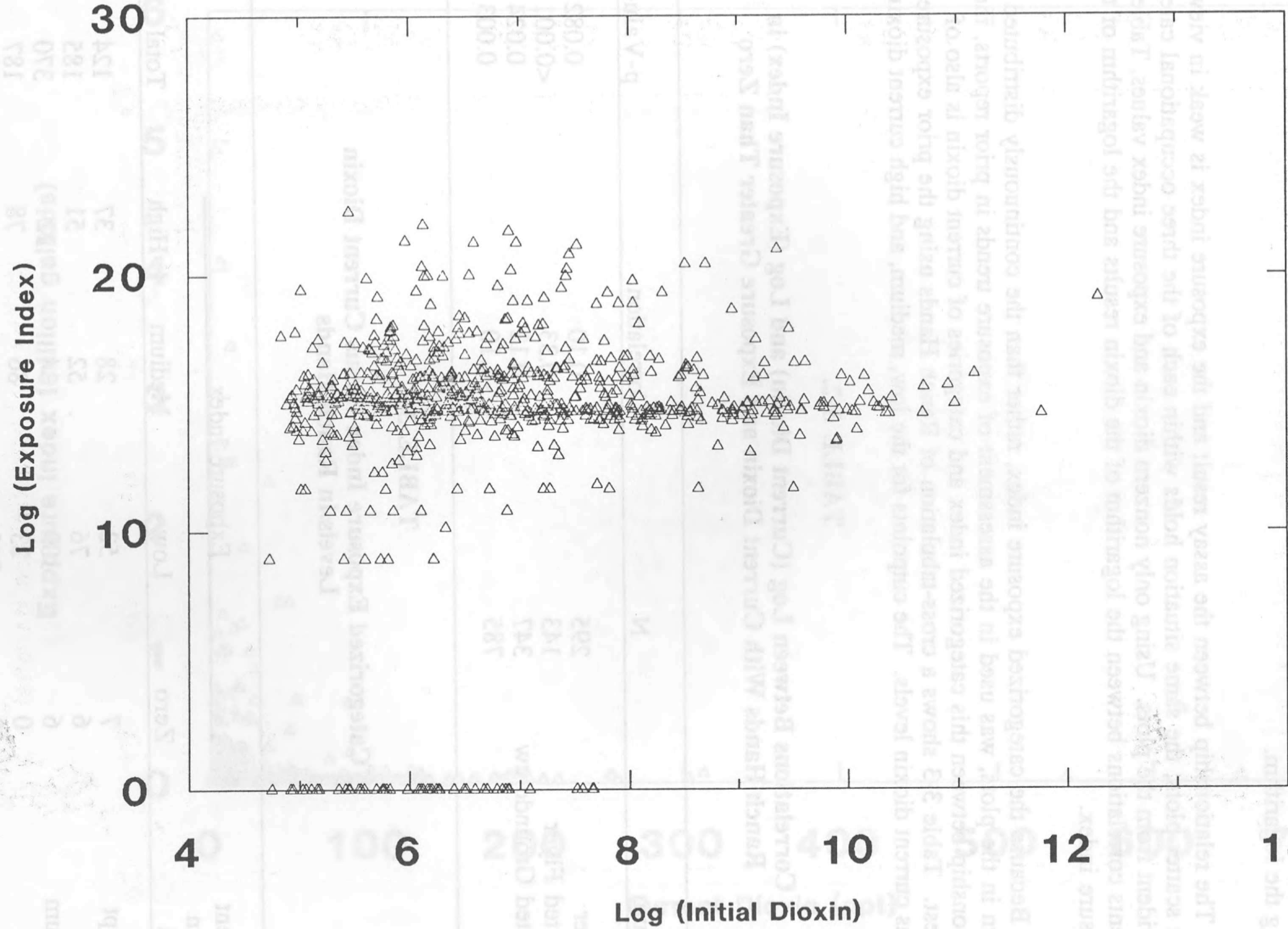

FIGURE 3-2. Logarithm of Initial Dioxin versus Logarithm of the Exposure Index in Ranch Hands With Current Dioxin Greater Than 5 ppt (N=742)

having a dioxin result are shown in Figures 3-3 and 3-4. Figures 3-5 through 3-7 show the logarithmic scatter plots within each of the three occupational strata (officer, enlisted flyer, enlisted groundcrew). One ppt was added to each current dioxin concentration value before taking the logarithm.

The relationship between the assay result and the exposure index is weak in view of these scatter plots; the same situation holds within each of the three occupational categories, as evident from the plots. Using only nonzero dioxin and exposure index values, Table 3-2 presents correlations between the logarithm of the dioxin results and the logarithm of the exposure index.

Because the categorized exposure index, rather than the continuously distributed index shown in the plots, was used in the assessment of exposure trends in prior reports, the relationship between this categorized index and categories of current dioxin is also of interest. Table 3-3 shows a cross-tabulation of Ranch Hands using the prior exposure index versus current dioxin levels. The cutpoints for the low, medium, and high current dioxin levels

TABLE 3-2.

Correlations Between Log (Current Dioxin) and Log (Exposure Index) in Ranch Hands With Current Dioxin and Exposure Greater Than Zero

Stratum	N	Correlation	p-Value
Officer	295	0.10	0.082
Enlisted Flyer	143	0.33	<0.001
Enlisted Groundcrew	347	0.12	0.024
All	785	-0.10	0.003

TABLE 3-3.

Categorized Exposure Index versus Current Dioxin Levels in Ranch Hands

Current Dioxin Level	Exposure Index				
	Zero	Low	Medium	High	Total
0-5 ppt	7	52	28	37	124
Low	6	76	52	51	185
Medium	6	109	134	121	370
High	0	23	86	78	187
Total	19	260	300	287	866

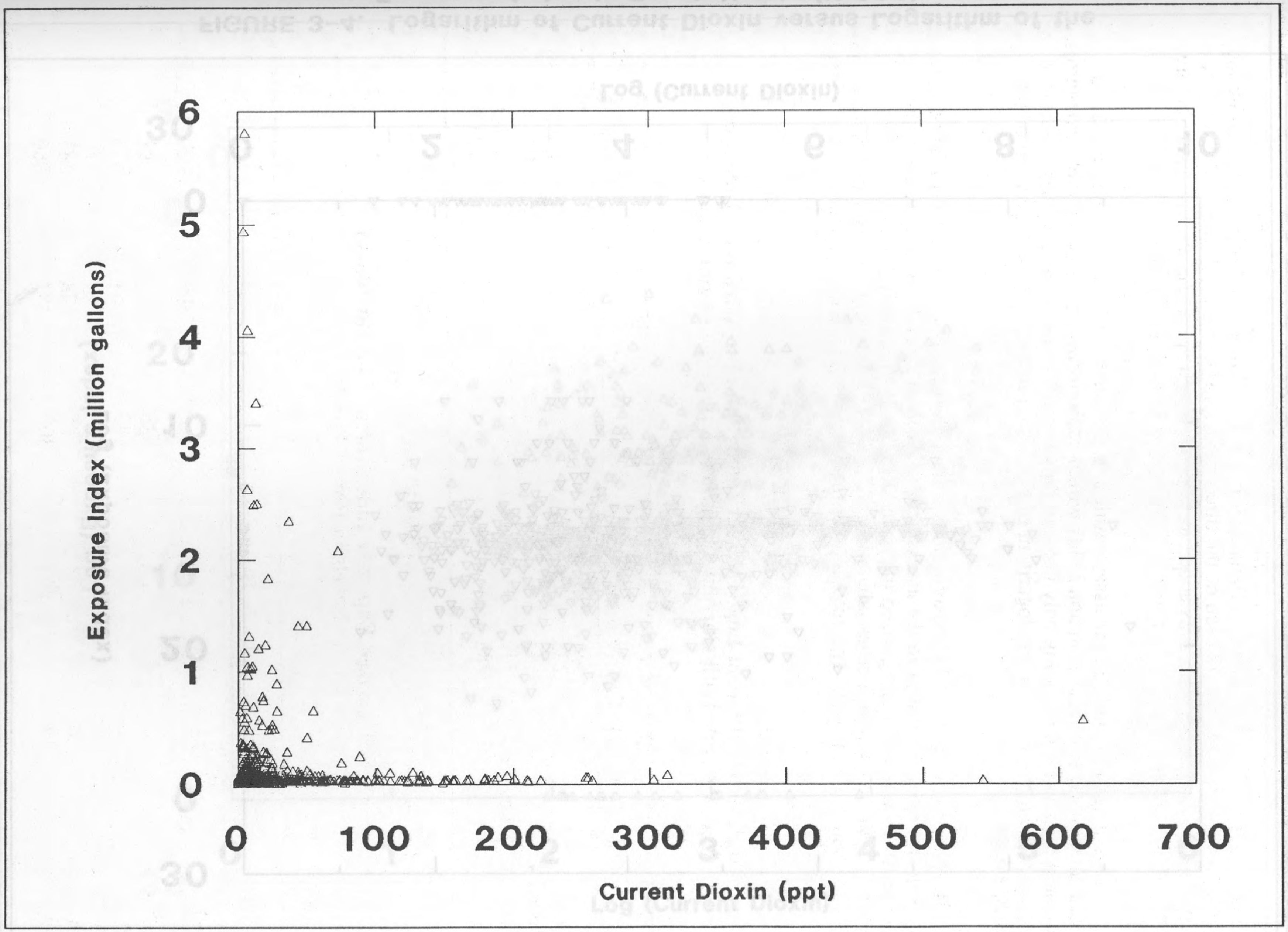

FIGURE 3-3. Current Dioxin versus the Exposure Index in Ranch Hands (N=866)

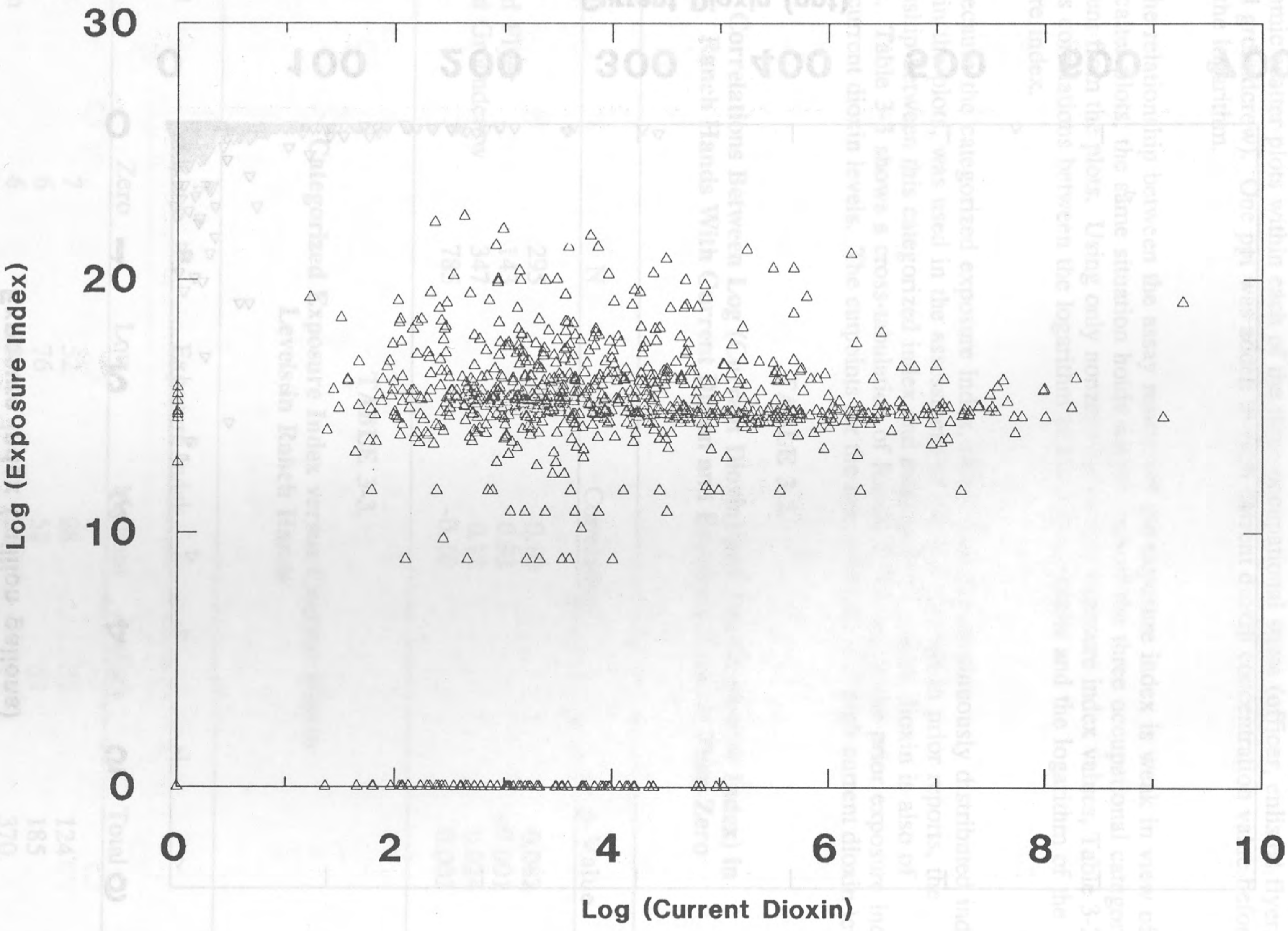

FIGURE 3-4. Logarithm of Current Dioxin versus Logarithm of the Exposure Index in Ranch Hands (N=866)

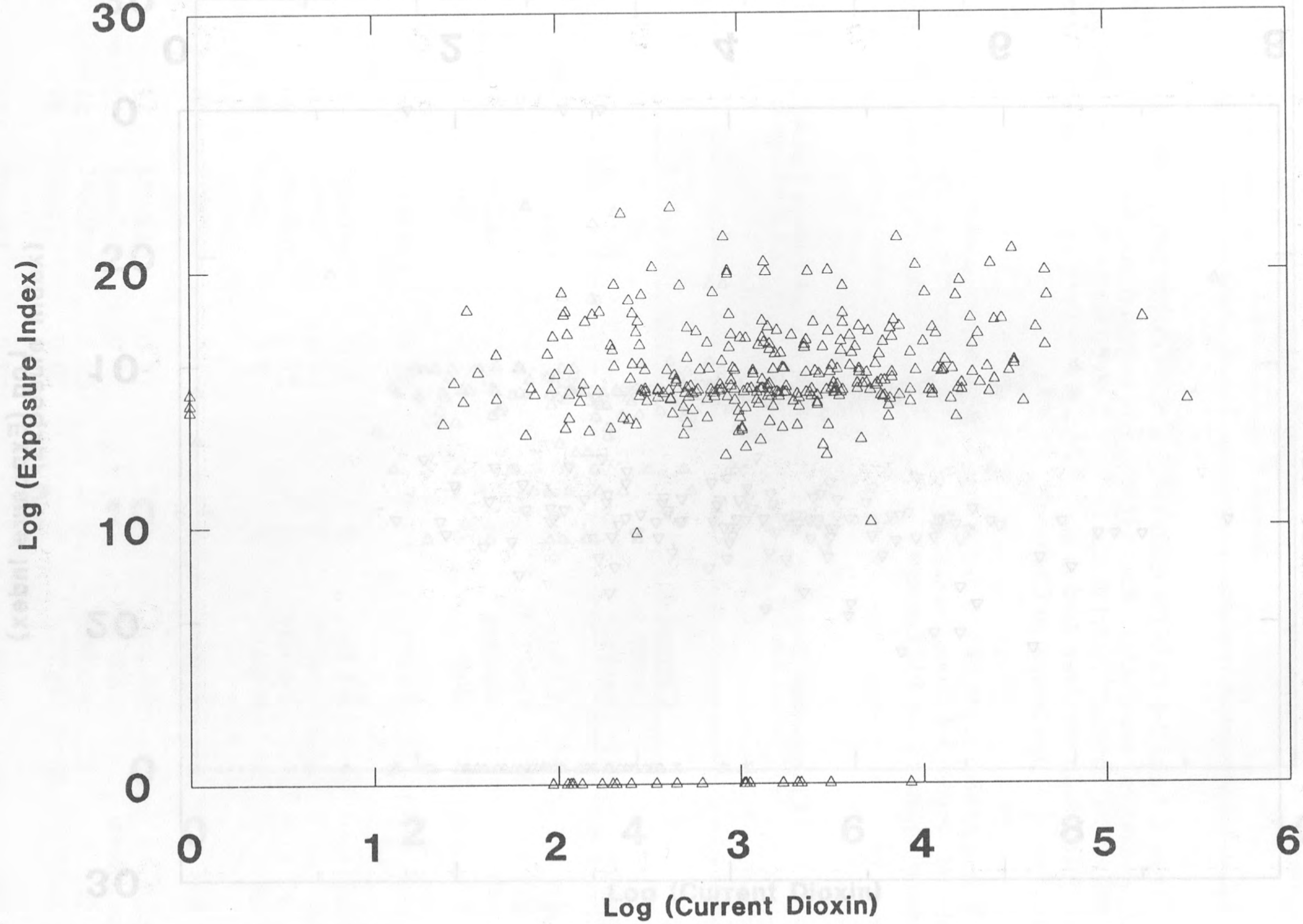

FIGURE 3-5. Logarithm of Current Dioxin versus Logarithm of the Exposure Index in Ranch Hand Officers (N=319)

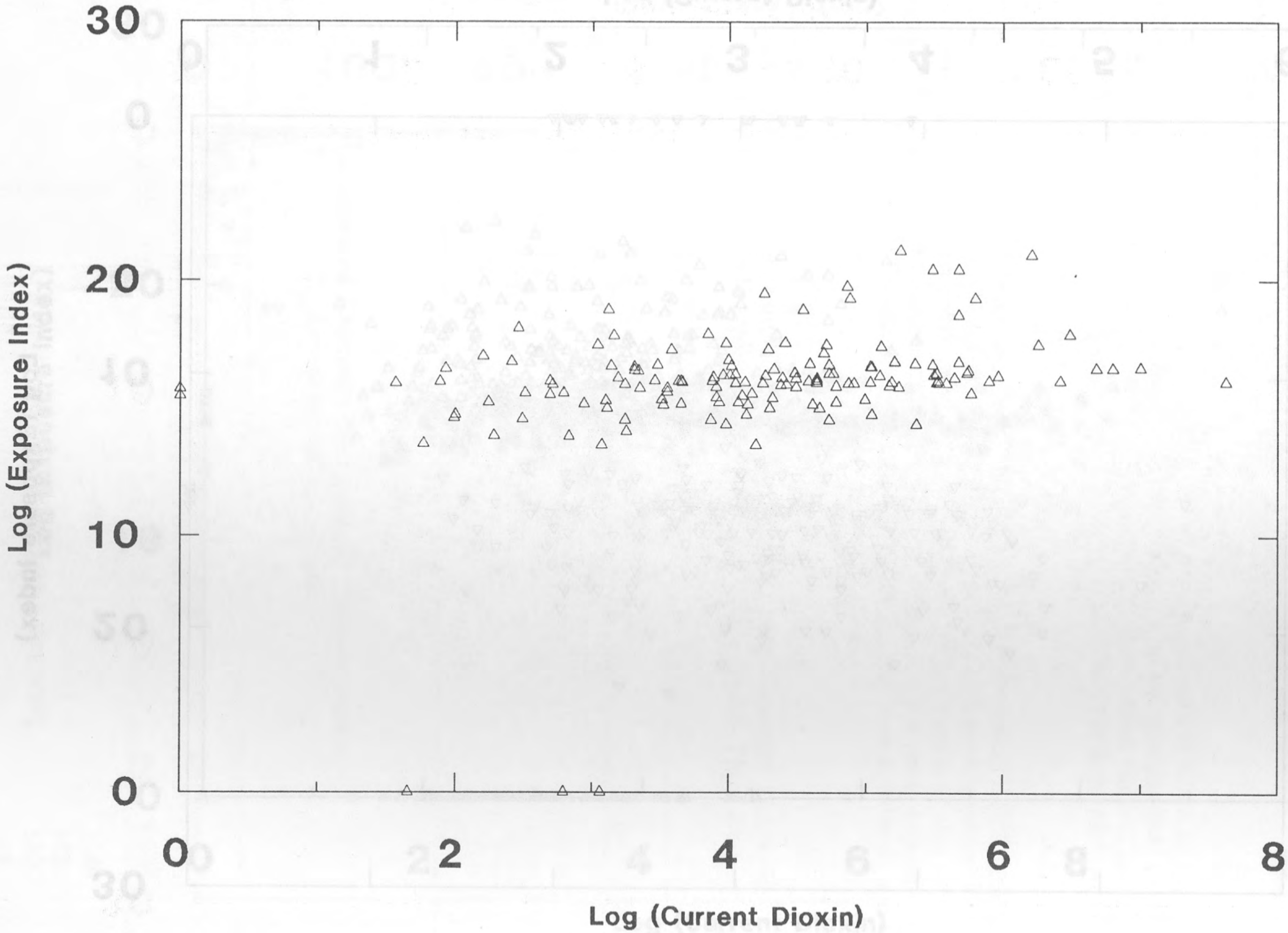

FIGURE 3-6. Logarithm of Current Dioxin versus Logarithm of the Exposure Index in Ranch Hand Enlisted Flyers (N=148)

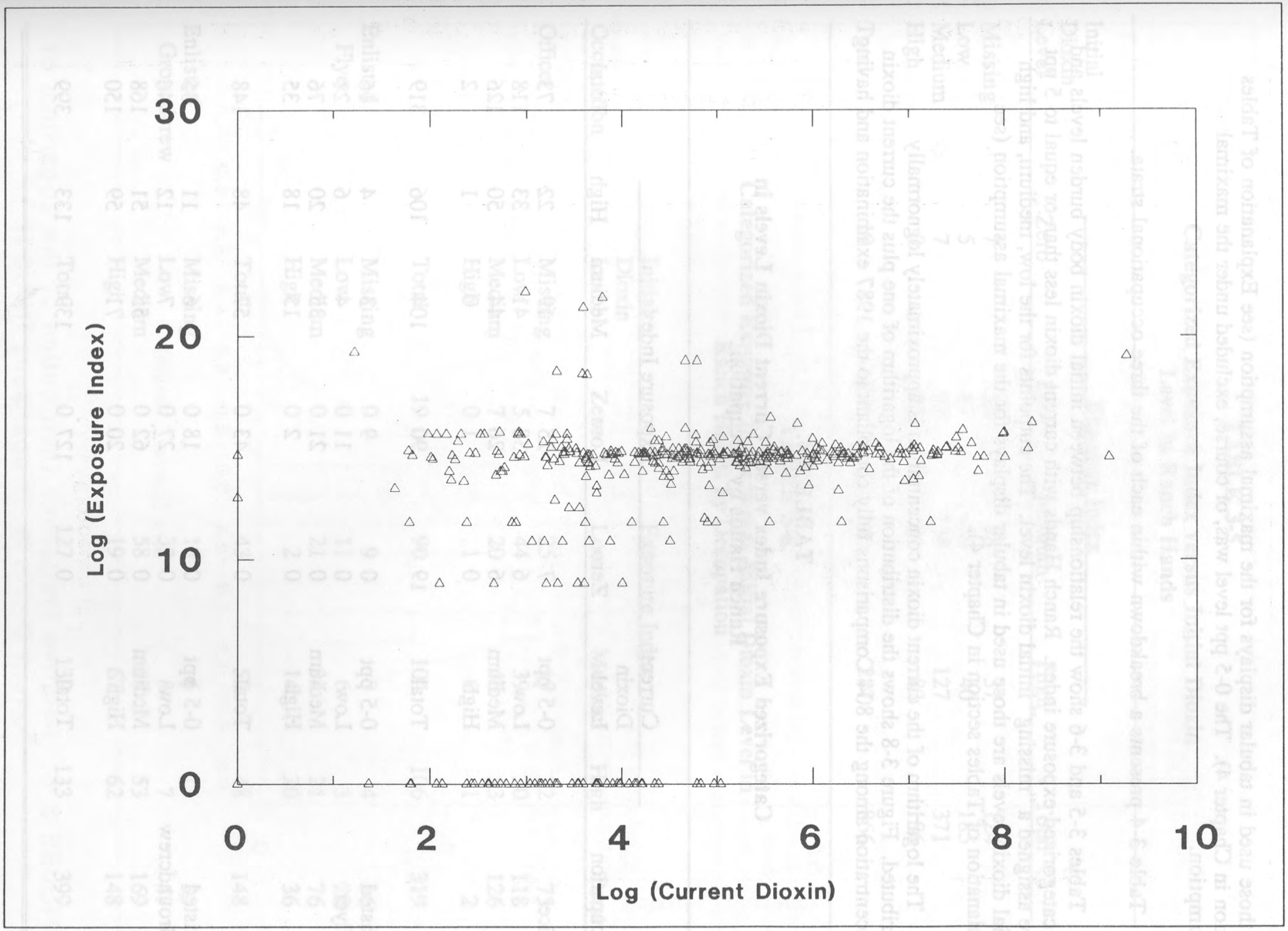

FIGURE 3-7. Logarithm of Current Dioxin versus Logarithm of the Exposure Index in Ranch Hand Enlisted Groundcrew (N=399)

are those used in tabular displays for the maximal assumption (see Explanation of Tables section in Chapter 4). The 0-5 ppt level was, of course, excluded under the maximal assumption.

Table 3-4 presents a breakdown within each of the three occupational strata.

Tables 3-5 and 3-6 show the relationship between initial dioxin body burden levels and the categorized exposure index. Ranch Hands with current dioxin less than or equal to 5 ppt were assigned a "missing" initial dioxin level. The cutpoints for the low, medium, and high initial dioxin levels are those used in tabular displays for the maximal assumption (see Explanation of Tables section in Chapter 4).

The logarithm of the current dioxin concentration is approximately lognormally distributed. Figure 3-8 shows the distribution of the logarithm of one plus the current dioxin concentration among the 804 Comparisons fully compliant to the 1987 examination and having

TABLE 3-4.

Categorized Exposure Index versus Current Dioxin Levels in Ranch Hands by Occupation

Occupation	Current Dioxin Level	Exposure Index				
		Zero	Low	Medium	High	Total
Officer	0-5 ppt	7	25	19	22	73
	Low	6	38	41	33	118
	Medium	6	26	44	50	126
	High	0	1	0	1	2
	Total	19	90	104	106	319
Enlisted Flyer	0-5 ppt	0	9	3	4	16
	Low	0	11	4	6	21
	Medium	0	21	35	20	76
	High	0	2	15	18	35
	Total	0	43	57	48	148
Enlisted Groundcrew	0-5 ppt	0	18	6	11	35
	Low	0	27	7	12	46
	Medium	0	62	55	51	168
	High	0	20	71	59	150
	Total	0	127	139	133	399

TABLE 3-5.

Categorized Exposure Index versus Initial Dioxin Level in Ranch Hands

Initial Dioxin Level	Exposure Index				
	Zero	Low	Medium	High	Total
Missing	7	52	28	37	124
Low	5	87	53	40	185
Medium	7	99	138	127	371
High	0	22	81	83	186
Total	19	260	300	287	866

TABLE 3-6.

Categorized Exposure Index versus Initial Dioxin Level in Ranch Hands by Occupation

Occupation	Initial Dioxin Level	Exposure Index				
		Zero	Low	Medium	High	Total
Officer	Missing	7	25	19	22	73
	Low	5	44	39	30	118
	Medium	7	20	46	53	126
	High	0	1	0	1	2
	Total	19	90	104	106	319
Enlisted Flyer	Missing	0	9	3	4	16
	Low	0	11	6	3	20
	Medium	0	21	34	21	76
	High	0	2	14	20	36
	Total	0	43	57	48	148
Enlisted Groundcrew	Missing	0	18	6	11	35
	Low	0	32	8	7	47
	Medium	0	58	58	53	169
	High	0	19	67	62	148
	Total	0	127	139	133	399

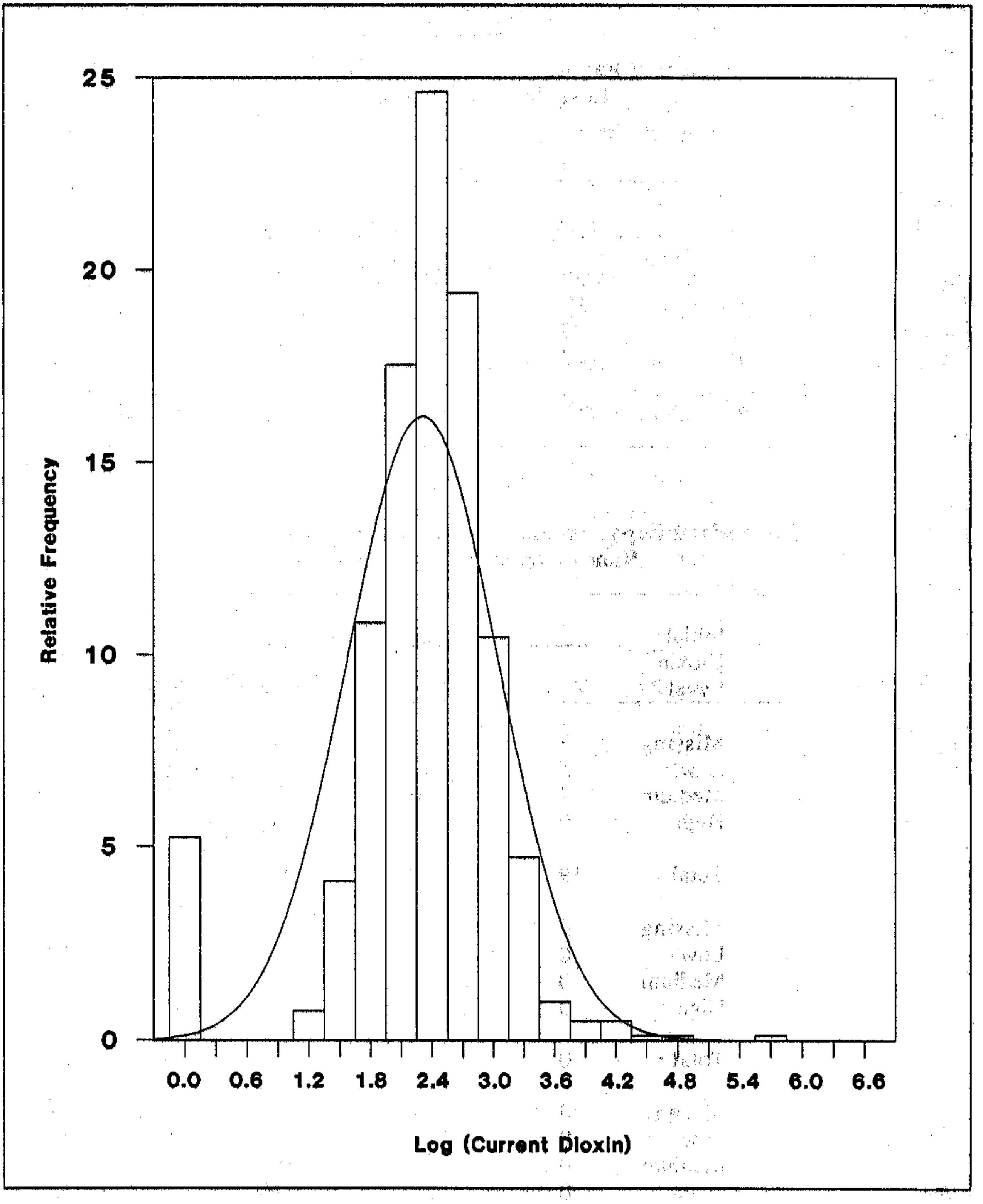

FIGURE 3-8. Relative Frequency Distribution of the Logarithm of Current Dioxin in Comparisons (N=804)

a dioxin assay result. A normal distribution was fit to these data and a multiple of the probability density function is plotted on the same graph. The fit is improved when the histogram is restricted to those Comparisons (n=762) having positive concentrations, as shown in Figure 3-9. The histogram of the logarithm of one plus current dioxin body burden in Ranch Hands is shown in Figure 3-10 with a multiple of the probability density function of the fitted normal distribution shown on the same plot.

SUMMARY

The indirectly calculated exposure index derived solely from personnel records and historical information has wide precedent in epidemiology. These data suggest that the work history-based exposure index methodology should be reconsidered in studies with exposures of short duration and low relative risks. The correlation between the AFHS exposure index and the dioxin body burden (current or initial levels) is weak although statistically significant. Cross tabulations of dioxin body burden levels versus the categorized exposure index, shown in Tables 3-2 through 3-6, indicate considerable misclassification if the dioxin measure (initial or current dioxin) is taken as the standard.

The dioxin measure is the preferred index of exposure because (a) it is a direct, rather than indirect measure of exposure, (b) the Ranch Hand levels appear logically placed relative to other cohorts, and (c) the within-occupation stratum levels appear to agree with exposure patterns described in Ranch Hand crew chief interviews conducted before the assay became available to participants in the AFHS.

Estimates of initial dioxin exposure will be improved with increased knowledge regarding its elimination in humans. New data in the Ranch Hand cohort and in people exposed to dioxin in Seveso, Italy, will be collected. The Seveso data will be used to evaluate the first-order elimination assumption. Variation in half-life with disease and changes in weight and body fat will be assessed with Ranch Hand data if the first-order elimination assumption (see Chapter 4) is supported by the Seveso data.

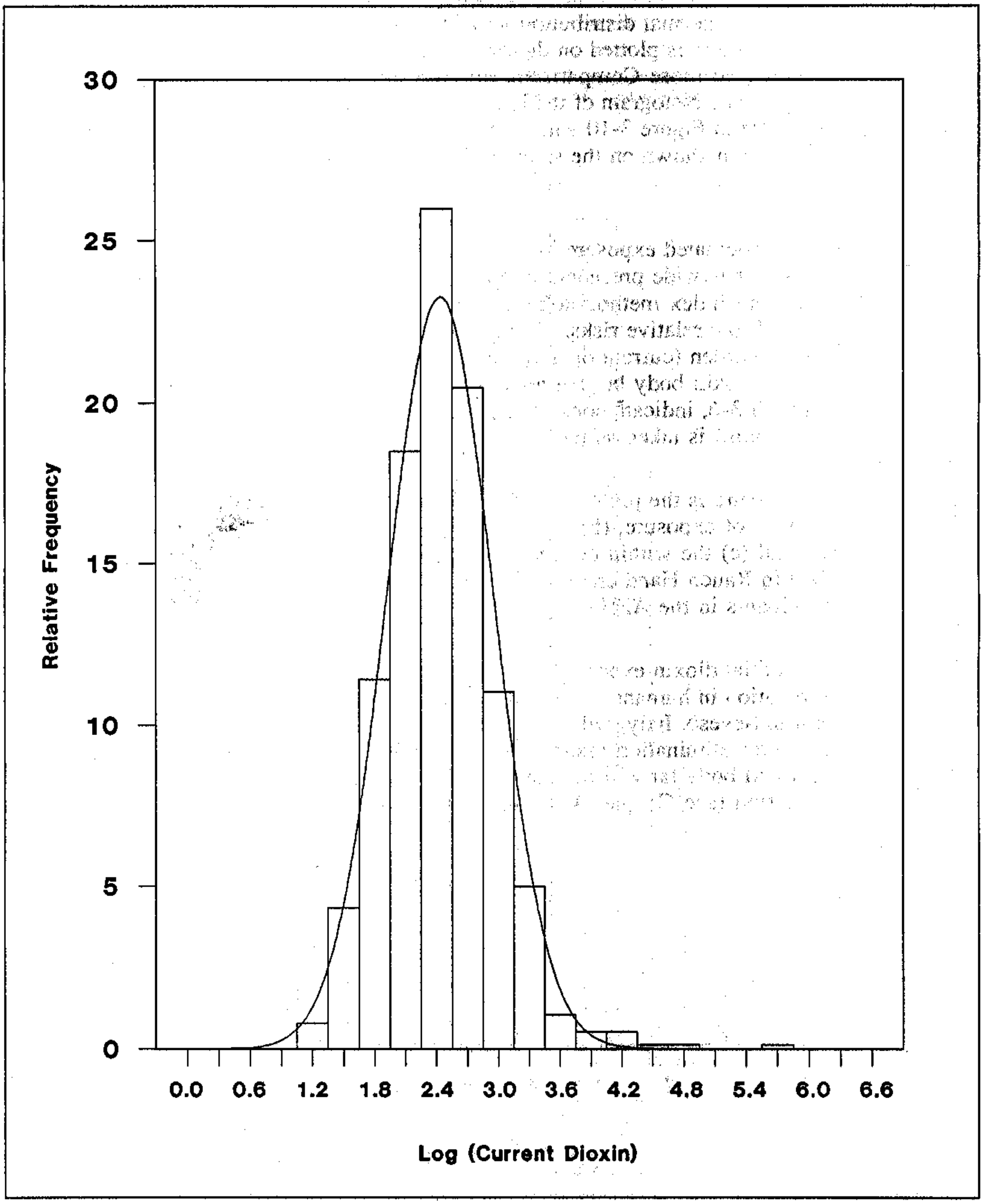

FIGURE 3-9. Relative Frequency Distribution of the Logarithm of Current Dioxin in Comparisons With Current Dioxin Greater Than Zero (N=762)

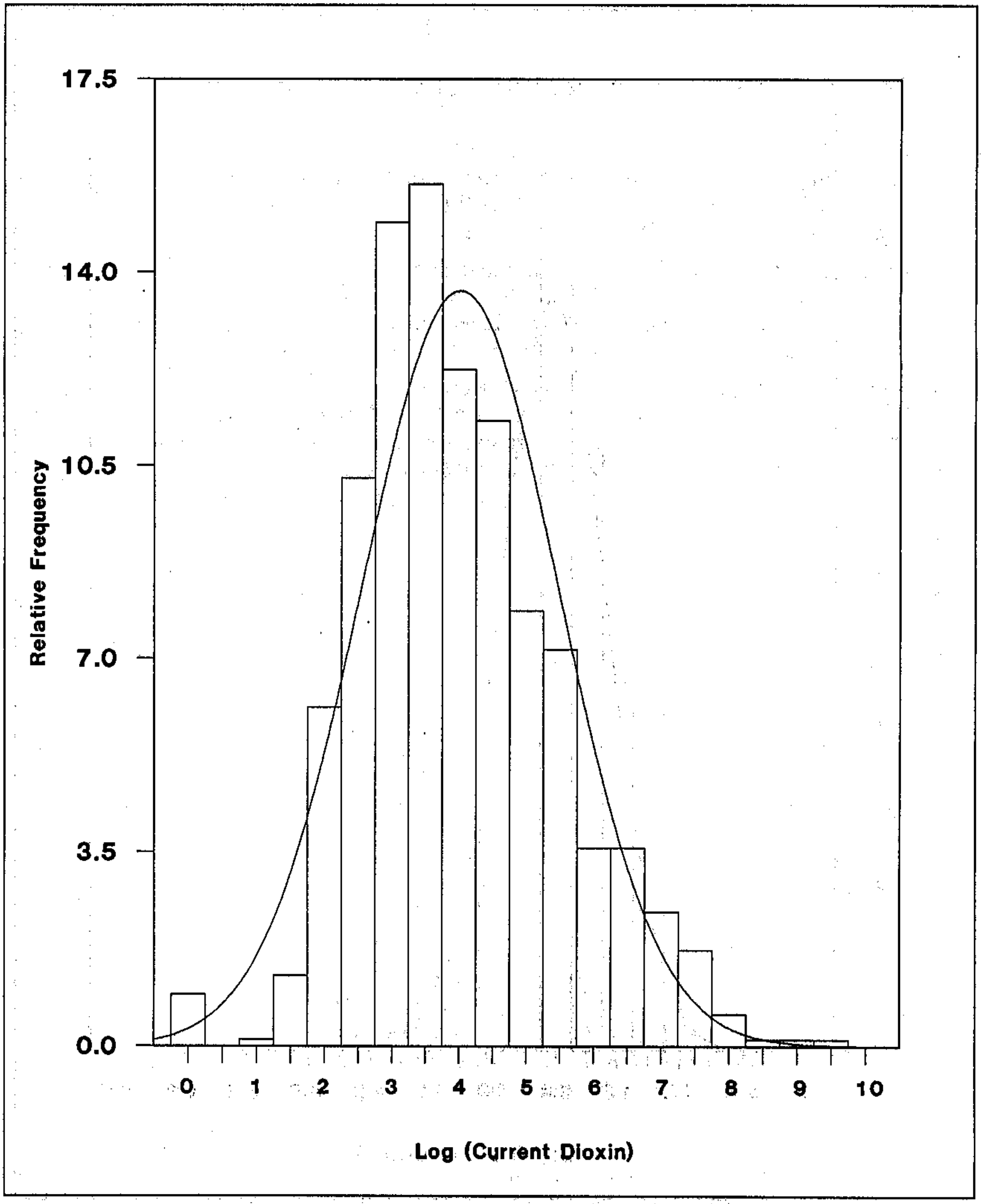

FIGURE 3-10. Relative Frequency Distribution of the Logarithm of Current Dioxin in Ranch Hands (N=866)

CHAPTER 3

REFERENCES

1. Young, A.L., J.A. Calcagni, C.E. Thalken, and J.W. Tremblay. 1978. The toxicology, environmental fate, and human risk of Herbicide Orange and its associated dioxin. Technical Report OEHL-TR-78-92, USAF Occupational and Environmental Health Laboratory, Brooks Air Force Base, Texas.

2. Mocharelli, P., D.G. Patterson, Jr., A. Marochi, and L.L. Needham. 1990. Pilot study (Phase II) for determining polychlorinated dibenzo-p-dioxin (PCDD) and polychlorinated dibenzofuran (PCDF) levels in serum of Seveso, Italy, residents collected at the time of exposure: Future plans. *Chemosphere* 20:967-74.

3. Patterson, D.G., Jr., M.A. Fingerhut, D.W. Roberts, L.L. Needham, M.H. Sweeney, D.A. Marlow, J.S. Andrews, W.E. Hulperin. 1989. Levels of polychlorinated dibenzo-p-dioxins and dibenzofurans in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *American Journal of Industrial Medicine* 16:135-46.

CHAPTER 4

STATISTICAL METHODS

This chapter summarizes statistical methods that were used for investigating relationships between serum dioxin measurements and health status of Ranch Hands and Comparisons. Current body burden dioxin levels were determined by the Centers for Disease Control (CDC) from serum samples taken from Ranch Hands and Comparisons. A variety of statistical procedures were applied to evaluate the relationships between specific health endpoints and dioxin, as measured from these serum samples.

MODELS AND ASSUMPTIONS

Prior Knowledge Regarding Dioxin

This study presents statistical analyses based on assumptions and models that were conceived in 1988 after the publication of the Ranch Hand dioxin pilot study and half-life substudy. At that time, available data regarding the elimination of dioxin in humans suggested that

- Measurements following the ingestion of dioxin by an individual showed that dioxin elimination appeared to be by first-order mechanisms (1).
- Air Force data on 36 Ranch Hand veterans with dioxin body burdens measured in blood drawn in 1982 and in 1987 produced a median half-life estimate of 7.1 years (2). The lack of correlation between individual half-lives and current dioxin levels supported the first-order elimination assumption.
- Assay results on 932 Ranch Hands and 888 Comparisons showed that the concentrations were lognormally distributed with the Ranch Hand distribution significantly shifted to the right of the Comparison distribution. The Comparison median was 4.2 ppt; the 98th percentile of the Comparison distribution was 10.17 ppt. The Ranch Hand median was 12.8 ppt and the 98th percentile was 168 ppt. Based on these data, levels at or below 10 ppt were considered background.

The term "elimination" denotes the overall removal of dioxin from the body. Some analyses in this report assume that the amount of dioxin in the body (C) decays exponentially with time according to the model $C = I \cdot \exp(-rT)$, where I is the initial level, $r = \log 2/H$, H is the half-life, and T is the time between the end of the Vietnam tour and the dioxin blood draw at the 1987 physical examination; this exponential decay law is termed first-order elimination in this report.

The first-order elimination assumption is not equivalent to assuming a one compartment model for dioxin distribution within the body. While a multicompartment model incorporating body composition and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) binding to tissue receptors would provide a detailed description of dioxin concentrations in different compartments, published multicompartment models for TCDD distribution within the body predict first-order elimination of TCDD, overwhelmingly due to fecal excretion (3). Direct assessment of the first-order assumption with serial dioxin results taken over many years on a number of exposed individuals has not been, as yet, carried out.

The term "body burden" refers to the serum lipid-weight concentration of TCDD, expressed in parts per trillion (4, 5). The lipid-weight dioxin measurement, also called current dioxin body burden in this report, is a derived quantity calculated from the formula ppt = ppq•102.6/W, where ppt is the lipid-weight concentration, ppq is the actual weight of dioxin in the sample in femtograms, 102.6 corrects for the average density of serum, and W is the total lipid weight of the sample (4).

The relationship between the serum lipid-weight concentration of dioxin and lipid-weight concentrations in adipose tissue is a subject of continuing research. The correlation between the serum lipid-weight concentration and adipose tissue lipid-weight concentration of dioxin has been observed by Patterson et al. to be 0.98 in 50 persons from Missouri (6). Using the same data, Patterson et al. calculated the partitioning ratio of dioxin between adipose tissue and serum on a lipid-weight basis as 1.09 (95% C.I.: [0.97,1.21]). On the basis of these data, a one-to-one partitioning ratio of dioxin between lipids in adipose tissue and the lipids in serum cannot be excluded. Measurements of dioxin in adipose tissue generally have been accepted as representing the body burden concentration of dioxin. The high correlation between serum dioxin levels and adipose tissue dioxin levels in the Patterson et al. study suggests that serum dioxin is also a valid measurement of dioxin body burden.

Fundamental Limitations of the Serum Dioxin Data

There are two evident limitations to the available data:

1) While Ranch Hand and ingestion data do not appear to violate a first-order elimination assumption, no serially repeated dioxin assay results taken over many years are available yet with which to evaluate directly the adequacy of the first-order elimination model in humans.
2) At this time, it has not been determined whether Ranch Hands with dioxin burdens at or below 10 ppt were exposed and their body burdens had decayed to background levels since their duty in Vietnam or whether they were not exposed at all during their tour in Vietnam.

Health versus Dioxin in Ranch Hands

Because first-order elimination is suggested, but not validated directly in humans, the dioxin versus health relationship was assessed within Ranch Hands using two models. The first model directly depends upon the first-order elimination assumption; the second does not. In combination, these two models circumvent the first fundamental limitation by assessing the dioxin versus health relationship with and without first-order elimination. Table 4-1 shows these two models, their assumptions, advantages, and disadvantages for a continuously distributed health variable y.

In Table 4-1, the phrase "single dioxin dose" is a simplification of the process by which Ranch Hands accumulated dioxin during their tour of duty in Vietnam. This process, which undoubtedly varied from individual to individual, is unknown. However, the Ranch Hand tours generally were short (1 to 3 years) relative to the time elapsed since their tours. Hence, additional knowledge regarding the accumulation of dioxin during an individual Ranch Hand's tour, were it to become available, likely would not change conclusions drawn from any of the statistical analyses presented in this report.

Analyses based on model 1 are dependent directly on the first-order elimination assumption, while those based on model 2 are not. With model 1 one assumes that elimination is first-order and that the half-life is 7.1 years for all Ranch Hands. With model 2 one assumes nothing about the kinetics of dioxin elimination other than Ranch Hands received a dose in Vietnam and that their body burdens have decreased in an unspecified manner with time. Thus, with model 1 one assumes "everything" is known about dioxin elimination in Ranch Hands; with model 2 one assumes "nothing" about dioxin elimination in Ranch Hands. All health data were analyzed with both models to reduce the likelihood that an effect would be missed due to incorrect assumptions regarding dioxin elimination.

The introduction of the time-by-current dioxin interaction term ($b_3 T \log_2 [C]$) in model 2 allows investigation of the dioxin health relationship with respect to time. For example, such an effect would be detected by model 2 if there was no relationship between health and dioxin in the first few years after exposure and a strong positive relationship many years after exposure. In this case, if the effect were strong enough, it would be detected by the interaction coefficient (b_3) being significantly different from zero. Following that, analyses within time strata would find the coefficient (b_1) of $\log_2$ (C) significantly different from zero and positive for large values of time (T); no significant difference between b_1 and 0 for small values of T would be found. It is important to note that a significant effect of this kind could be due to the passage of time or to a higher initial dioxin level received by Ranch Hands in the later time stratum or both of these.

Analyses based on models 1 and 2 were carried out both adjusted and unadjusted for covariates.

No additional data or other information exist to determine whether any of the Ranch Hands with background levels (≤10 ppt) of current dioxin (n=345) received a dose above background levels in Vietnam. To accommodate this lack of knowledge, all analyses based on models 1 and 2 were carried out with these Ranch Hands excluded. Additionally, since 10 ppt may be considered arbitrary or too conservative, all analyses based on models 1 and 2 were carried out with Ranch Hands having less than or equal to 5 ppt (n=124) excluded. With the second approach, it is assumed that Ranch Hands currently having more than 5 ppt (the approximate Comparison median) were exposed in Vietnam and those with less than 5 ppt were not. These two assumptions are termed "minimal" (Ranch Hands with more than 10 ppt were exposed in Vietnam) and "maximal" (Ranch Hands with more than 5 ppt were exposed in Vietnam).

TABLE 4-1.

Models 1 and 2 for Assessing Health versus Dioxin in Ranch Hands Only: Assumptions, Advantages, and Disadvantages

---

Model 1: $y = \beta_0 + \beta_1 \log_2(I) + e$

where

- y = health variable
- I = extrapolated initial dose, assuming first-order elimination, $I = C \cdot \exp(\log 2 \cdot T/H)$
- T = time between the end of the Vietnam Ranch Hand tour of duty and the 1987 physical examination
- C = current dioxin body burden, determined in 1987
- H = dioxin half-life in Ranch Hands assuming first-order elimination (7.1 years)
- e = zero mean normal error

Assumptions:	Ranch Hands received a single dioxin dose in Vietnam and background exposure thereafter.
	Ranch Hands experienced first-order dioxin elimination with a constant known half-life of 7.1 years.
	The error variance does not change with health status (y) or initial dioxin dose (I).
Advantages:	Easily interpretable.
	Most efficient if first-order elimination and constant half-life are valid assumptions and y is linearly related to $\log_2(I)$
Disadvantages:	Will be biased if first-order elimination or constant half-life assumption is not valid.
	Does not address time-related effects.

TABLE 4-1. (Continued)

Models 1 and 2 for Assessing Health versus Dioxin in Ranch Hands Only: Assumptions, Advantages, and Disadvantages

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Model 2: $y = \beta_0 + \beta_1 \log_2(C) + \beta_2 T + \beta_3 T \log_2(C) + e$

where

- y = health variable
- T = time between the end of the Vietnam Ranch Hand tour of duty and the 1987 physical examination
- C = current dioxin body burden, determined in 1987
- e = zero mean normal error

Assumptions:	Ranch Hands received a single dioxin dose in Vietnam and background exposure thereafter.
	Ranch Hand dioxin body burdens changed with time (T) in the same way for all individuals.
	The dioxin versus health relationship may change with time (T).
	The error variance does not change with values of the health variable (y), the current dioxin body burden (C), time (T), or the product of time and the logarithm of the current dioxin body burden (T $\log_2$[C]).
Advantages:	Does not depend on any particular elimination law or half-life assumptions.
	Assesses time-related effects.
Disadvantages:	Less easily interpreted than model 1.
	Less efficient than model 1 if first-order elimination and constant half-life are valid assumptions and y is linearly related to $\log_2$(I).
	Biased if any of the assumptions are violated.

In summary, to address the second fundamental limitation, two assumptions about Ranch Hands with current dioxin body burdens less than 10 ppt were made. These minimal and maximal assumptions are

- *Minimal assumption: Ranch Hands with less than or equal to 10 ppt were not exposed to dioxin in Vietnam*
- *Maximal assumption: Ranch Hands with less than or equal to 5 ppt were not exposed to dioxin in Vietnam.*

The terms minimal and maximal were given because fewer Ranch Hands were exposed under the minimal than under the maximal assumption. The numbers 5 and 10 correspond to the approximate median and 98th percentile of the Comparison current dioxin distribution. Based on this Comparison dioxin distribution, current dioxin levels less than 10 ppt are called background levels.

To assess the dioxin versus health relationship while addressing the second fundamental limitation, all analyses based on models 1 and 2 were carried out under the minimal and again under the maximal assumptions. Under the minimal assumption, Ranch Hands with less than or equal to 10 ppt were excluded from the analyses. Under the maximal assumption, Ranch Hands with less than or equal to 5 ppt were excluded from the analyses.

Table 4-2 shows counts of exposed Ranch Hands under the minimal and maximal assumptions with initial and current dioxin trichotomized for tabular presentation. Ranch Hands under the maximal assumption are termed the "maximal cohort"; those under the minimal assumption are termed the "minimal cohort." The time between the end of tour and the 1987 physical examination is dichotomized at 18.6 years (corresponding approximately to the year 1969), the approximate median of the maximal cohort. The cutpoints for stratifying dioxin levels (I and C) were the approximate 25th and 75th percentiles and were specific to a particular cohort.

Health versus Dioxin in Ranch Hands and Comparisons

Finally, an assessment of the health consequences of current dioxin body burdens above background was carried out with a third model (model 3) that required no assumptions about when or how increased dioxin body burdens were attained and was applied to both Ranch Hand and Comparison data. This model assessed health versus categorized current dioxin body burden (D) with four levels, found in Table 4-3.

The cutpoint between the low and high categories, 33.3 ppt, is the approximate median dioxin level of Ranch Hands having more than 15 ppt. Ranch Hands having between 10 ppt and 15 ppt were excluded from these categorized dioxin analyses in an attempt to avoid misclassification of Ranch Hands to the unknown and low categories due to various sources of variation in the dioxin measurement.

Table 4-4 shows counts of participants within each level of categorized current dioxin. The relationship between current health and categorized dioxin body burden was based on the model shown in Table 4-5.

TABLE 4-2.

Ranch Hand Sample Sizes Under the Minimal and Maximal Assumptions

		Initial Dioxin (I)		Current Dioxin (C)		
Assumption	Stratum Name	Stratum	Count	Stratum	T≤18.6 Count	T>18.6 Count
Minimal	Low	52<I≤93	130	10<C≤14.65	72	58
	Medium	93<I≤292	260	14.65<C≤45.75	128	132
	High	292<I	131	45.75<C	54	77
		Total	521		254	267
Maximal	Low	25<I≤56.9	185	5<C≤9.01	106	79
	Medium	56.9<I≤218	371	9.01<C≤33.3	191	179
	High	218<I	186	33.3<C	83	104
		Total	742		380	362

TABLE 4-3.

Current Dioxin Body Burden (D) Categorized in Ranch Hands and Comparisons for Model 3

Value	Definition
Background	Comparisons with up to 10 ppt
Unknown	Ranch Hands with up to 10 ppt
Low	Ranch Hands with more than 15 and up to 33.3 ppt
High	Ranch Hands with more than 33.3 ppt

TABLE 4-4.

Counts of Participants by Level of Categorized Current Dioxin (D)

Level	Count
Background	786
Unknown	345
Low	196
High	187
Total	1,514

TABLE 4-5.

Model 3 for Assessing Health versus Categorized Current Dioxin Body Burden in Ranch Hands and Comparisons

Model 3: $y = \beta_0 + \beta_1 D + e$

where

y = health variable
D = categorized current dioxin
e = zero mean normal error

Assumptions: Dioxin body burden has accumulated with time. The error variance does not change with categorized current dioxin body burden (D).

Advantage: Requires no assumption regarding the time course of dioxin accumulation or elimination.

Disadvantages: Makes no use of prior belief that Ranch Hands received an unusually large dioxin dose in Vietnam. Does not address time-related effects.

In addition to assessing the overall mean change in the health variable (y) with levels of categorized current dioxin (D), the mean values of y within the unknown, low, and high categories were contrasted with the mean values of y within the background category.

Figure 4-1 summarizes the current dioxin levels used in models 1, 2, and 3.

Data Error

After the serum dioxin analyses were well underway, an error was discovered with respect to the race of one Comparison. The participant (subject 36410) was listed in the data base as a non-Black when in fact he was a Black. The Comparison was a 49-year-old at the Baseline examination and he was a member of the enlisted groundcrew cohort. His current serum dioxin value was 3.97 ppt as determined from the assay performed on the 1987 examination serum sample. The following abnormal medical conditions were noted for this individual: hepatomegaly, reported and verified hypertension, hyperpigmentation, and acne. The data error was corrected for the cardiovascular, malignancy, and dermatology assessments. Because the individual was a Comparison only the model 3 analyses of the other clinical area assessments were affected.

Bias Calculations

In any epidemiologic study, investigators must be concerned with avoiding spurious conclusions that are attributable to limitations in study design or analysis. The introduction of the dioxin assay as the measure of exposure in this study has provided the best available information regarding dioxin exposure in Ranch Hands and Comparisons. Uncertainties remain, however, regarding the choice of statistical models with which to assess the relationship between dioxin and health.

Biased results will be produced if the assumptions underlying any of the three statistical models are violated. Of the three models, model 1 is the most vulnerable to this kind of bias, since it depends directly on two unvalidated assumptions: (a) that dioxin elimination is first-order and (b) all Ranch Hands eliminate dioxin at the same rate (all Ranch Hands have the same dioxin half-life of 7.1 years). Air Force investigators currently are gathering additional data to evaluate both assumptions. The original half-life study on 36 Ranch Hands is being expanded to approximately 500 Ranch Hands. Assuming that dioxin elimination is first-order, this larger study will allow an assessment of half-life variability with weight changes, percent body fat changes, and disease since exposure. Additionally, the Air Force is collaborating with the CDC and Italian health authorities to assay serum collected periodically from people exposed in the Seveso accident. These data will consist of five dioxin measurements taken over a period of 10 years on 20 males who were adults at the time of the accident and will allow, for the first time, a direct assessment of the first-order elimination assumption in humans.

Until the Ranch Hand half-life study is expanded, the only available information regarding half-life variation in Ranch Hands is that derived from the smaller cohort of 36 subjects. Unpublished analyses of half-life heterogeneity among those 36 Ranch Hands suggest that half-life varies with relative weight changes between 1982 and 1987. With relative weight changes dichotomized at the median (2.7%), the 18 Ranch Hands below the median have an estimated half-life of 9.7 years (95% C.I.: [6.8,17.3]) and the 18 Ranch

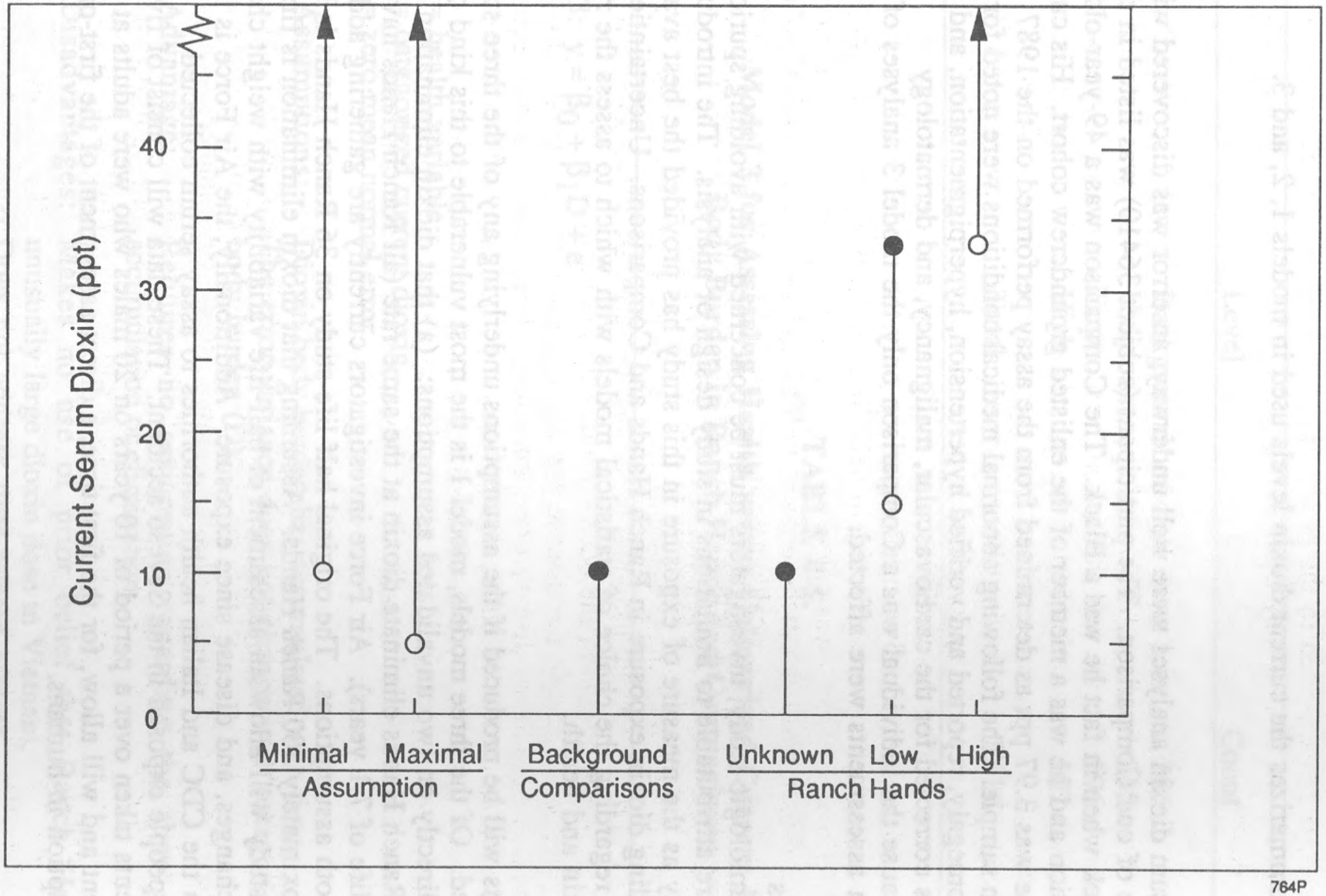

FIGURE 4-1. Ranges of Current Serum Dioxin Levels Used in Different Analysis Models

Hands above the median have an estimated half-life of 6.2 years (95% C.I.: [5.0,8.0]). The analysis showed a significant difference between these two half-lives (p=0.02). The two confidence intervals overlap because they are not derivable from the test for equality of half-lives. "Apparent" half-life decreases may be due to weight gain because of dilution of the body burden when it is redistributed to the new adipose tissue. Conversely, when there has been weight loss, the body burden may be redistributed in less adipose tissue and the serum concentration increases.

If these results are generalized to all Ranch Hands, statistical inference based on model 1 will be biased. For example, if the first-order elimination assumption is valid, but the constant half-life assumption is not, and there is no misclassification with regard to health status, odds ratios expressing the relationship between health and dioxin based on model 1 will be biased toward unity. That is, a misspecification of a constant half-life when, in fact, half-life changes with weight changes, will lead to misclassification with regard to dioxin level and therefore reduce our ability to detect an association between health and dioxin. To evaluate this possibility, the bias induced in the odds ratio under the maximal assumption and the computation of initial dioxin body burden assuming a constant half-life of 7.1 years (when in fact 50 percent of Ranch Hands have a dioxin half-life of 6 years and the other 50 percent have a dioxin half-life of 10 years) was calculated (7). In carrying out this calculation, it was assumed that initial dioxin had been dichotomized to high and low, with Ranch Hands assigned to the high category if their calculated initial dioxin level was greater than 218 ppt and assigned to the low category if their level was less than 218 ppt. The sample sizes of the real maximal cohort were used in the calculation; 186 Ranch Hands had a high initial dose and 556 had a low initial dose. With these assumptions, 76.3 percent of Ranch Hands assigned to the high category and 6.1 percent assigned to the low category truly had an initial dose above 218 ppt. The resultant bias in the odds ratio due to this misclassification depends on the true value of the odds ratio and the disease prevalence in the low category. For example, if the true odds ratio is 2.0 and the disease prevalence in the low initial dioxin category is 5 percent, this misclassification will produce an odds ratio of 1.7. Table 4-6 shows other values of the biased odds ratio produced by this misclassification for true odds ratios from 1 to 3 and the disease prevalence in the low initial dioxin category held fixed at 5 percent. There is no bias under assumptions if there is no association between initial dioxin and disease (true odds ratio equal to 1.0).

Model 2 also may be biased if, as suggested by the weight change analysis on the 36 Ranch Hands in the half-life study, 50 percent of Ranch Hands are fast dioxin eliminators (having a short half-life) and 50 percent of Ranch Hands are slow eliminators (with a longer half-life). If this attribute is not taken into account in the analysis (such as through adjustment for relative weight change), then the odds ratio relating disease to dioxin exposure will be biased toward unity. Again, disease status is assumed to be determined without error. For example, if slow eliminators experience an effect that does not become expressed until 20 years after exposure, if fast eliminators do not experience the effect, and if the analysis is not adjusted for relative weight change, then the ability of the model to detect the effect will be attenuated by the lack of adjustment. The extent of this bias toward the null depends on the nature of the four-factor interaction between health, current dioxin, time, and relative weight change, as well as upon the disease prevalence among Ranch Hands with low dioxin levels at each combination of categories of time and relative weight change. Bias calculations for this scenario, therefore, are more complicated and speculative than those presented for model 1 and were not pursued further.

TABLE 4-6.

Biased Odds Ratios Produced by a Misspecification of the Half-Life in the Calculation of the Initial Dioxin Body Burden in Model 1, Assuming a Disease Prevalence of 5 Percent in Ranch Hands Having a Low Calculated Initial Dose

True Odds Ratio	Biased Odds Ratio
1.0	1.0
1.5	1.3
2.0	1.7
2.5	2.0
3.0	2.2

Model 3 requires fewer assumptions than models 1 or 2, but is susceptible to bias due to misclassification or incorrect modeling. Biased results most likely are to occur with model 3 due to the failure to adjust for an important covariate. Every attempt, however, has been made in this report to adjust for all known important covariates.

The Correlation Between Initial Dioxin and Current Dioxin

The extrapolated initial dioxin dose is correlated highly with current dioxin level (correlation coefficient >0.98 for both the minimal and maximal cohorts). The same high correlation is, of course, seen between the logarithms of these quantities. The reason for the high correlation is that the initial dioxin dose is the current dioxin body burden multiplied by 2 raised to the power T/7.1. This high correlation is simply an expression of the fact that if the first-order model is valid and if dioxin half-life is constant, then models 1 and 2 nearly are redundant because the variation of time (T) is relatively small (see Figure 4-2).

FACTORS DETERMINING ANALYTICAL METHOD

For a specified questionnaire-based or clinical measurement determined from the physical or laboratory examination, the selection of an analytical method was dependent on each of the following:

- Dependent Variable Form — Continuous or discrete
- Serum Dioxin Estimate — Initial dioxin, current dioxin and time since tour, or categorized current dioxin incorporating group membership
- Analysis Type — Unadjusted, adjusted, or longitudinal

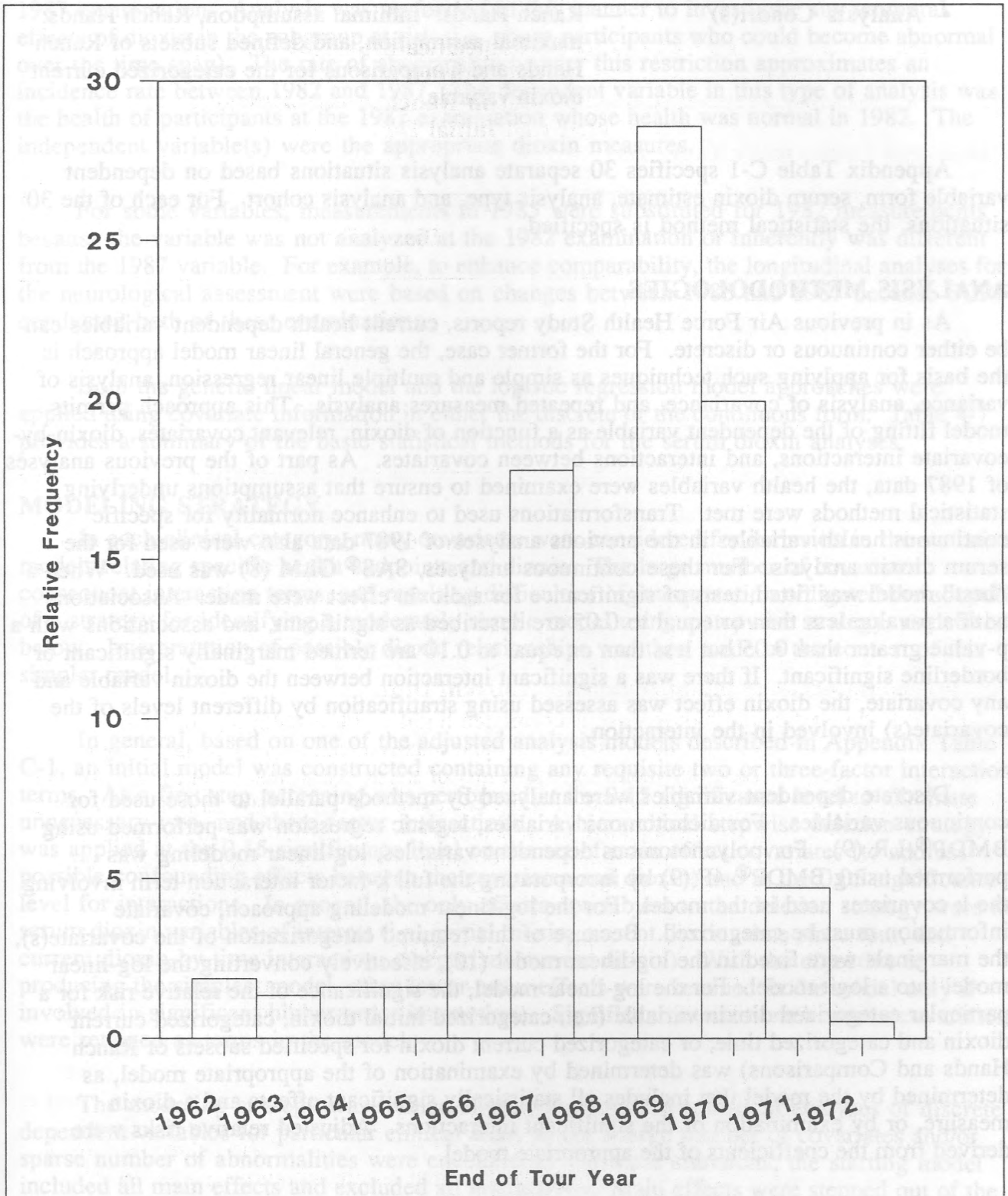

FIGURE 4-2. Relative Frequency Distribution of End of Tour Year in Ranch Hands Under the Maximal Assumption (N=742)

- Analysis Cohort(s) — Ranch Hands: minimal assumption, Ranch Hands: maximal assumption, and defined subsets of Ranch Hands and Comparisons for the categorized current dioxin variable.

Appendix Table C-1 specifies 30 separate analysis situations based on dependent variable form, serum dioxin estimate, analysis type, and analysis cohort. For each of the 30 situations, the statistical method is specified.

ANALYSIS METHODOLOGIES

As in previous Air Force Health Study reports, current health dependent variables can be either continuous or discrete. For the former case, the general linear model approach is the basis for applying such techniques as simple and multiple linear regression, analysis of variance, analysis of covariance, and repeated measures analysis. This approach permits model fitting of the dependent variable as a function of dioxin, relevant covariates, dioxin-by-covariate interactions, and interactions between covariates. As part of the previous analyses of 1987 data, the health variables were examined to ensure that assumptions underlying statistical methods were met. Transformations used to enhance normality for specific continuous health variables in the previous analyses of 1987 data also were used for the serum dioxin analysis. For these continuous analyses, SAS® GLM (8) was used. When a "best" model was fitted, tests of significance for a dioxin effect were made. Associations with a p-value less than or equal to 0.05 are described as significant, and associations with a p-value greater than 0.05 but less than or equal to 0.10 are termed marginally significant or borderline significant. If there was a significant interaction between the dioxin variable and any covariate, the dioxin effect was assessed using stratification by different levels of the covariate(s) involved in the interaction.

Discrete dependent variables were analyzed by methods parallel to those used for continuous variables. For dichotomous variables, logistic regression was performed using BMDP®-LR (9). For polychotomous dependent variables, log-linear modeling was performed using BMDP®-4F (9) by incorporating the full k-factor interaction term involving the k covariates used in the model. For the log-linear modeling approach, covariate information must be categorized. Because of this required categorization of the covariate(s), the marginals were fixed in the log-linear model (10), effectively converting the log-linear model into a logit model. For the log-linear model, the significance of the relative risk for a particular categorized dioxin variable (i.e., categorized initial dioxin, categorized current dioxin and categorized time, or categorized current dioxin for specified subsets of Ranch Hands and Comparisons) was determined by examination of the appropriate model, as determined by the model that includes all statistically significant effects and a dioxin measure, or by examination of the significant interactions. Adjusted relative risks were derived from the coefficients of the appropriate model.

Selected longitudinal analyses were performed investigating changes in health status between 1982 and 1987, for each of the three dioxin analysis models. The variables selected for longitudinal study were chosen prior to all 1987 examination data analyses. In the longitudinal analysis of discrete variables, only those participants whose health was classified as normal in 1982 were included in the analysis of the participants' health at the

1987 examination. Analysis was performed in this manner to investigate any temporal effects of dioxin in the subgroup at risk (i.e., those participants who could become abnormal over the time span). The rate of abnormalities under this restriction approximates an incidence rate between 1982 and 1987. The dependent variable in this type of analysis was the health of participants at the 1987 examination whose health was normal in 1982. The independent variable(s) were the appropriate dioxin measures.

For some variables, measurements in 1985 were substituted for 1982 measurements because the variable was not analyzed at the 1982 examination or inherently was different from the 1987 variable. For example, to enhance comparability, the longitudinal analyses for the neurological assessment were based on changes between 1985 and 1987 because SCRF conducted both of these examinations.

Both the general linear model and the logistic regression model approaches were applied using covariate information in either the discrete or the continuous form. Table 4-7 provides a summary of the basic statistical methods for the serum dioxin analyses.

MODELING STRATEGY

In each clinical category, many covariates were considered for inclusion in the statistical models relating specific health endpoints and dioxin. The large number of covariates, consequent interaction terms, and resulting difficulties of interpretation obligated the adoption of a strategy for identifying a moderately simple model using a stepwise strategy, as defined below. Interpretation of possible dioxin relationships was then made in the context of this simpler model.

In general, based on one of the adjusted analysis models described in Appendix Table C-1, an initial model was constructed containing any requisite two or three-factor interaction terms. As a first step, screening was performed at the 0.15 significance level to eliminate unnecessary two- and three-factor interactions. A hierarchical stepwise deletion strategy was applied at the 0.15 significance level on the set of main effect covariates (to address possible confounding effects between the covariates and dioxin) and at the 0.05 significance level for interactions. In general, the only effects not subject to the deletion strategy were the serum dioxin variables of interest (i.e., initial dioxin; current dioxin, time since tour, and current dioxin-by-time interaction; categorized current dioxin). With the objective of producing the simplest model, other lower-order effects were retained in the model only if involved in significant higher-order interactions. Significant interactions between covariates were retained as terms in the model.

The modeling strategy was refined slightly for adjusted statistical analyses of discrete dependent variables for particular clinical areas where a large number of covariates and/or sparse number of abnormalities were encountered. In these situations, the starting model included all main effects and excluded all interactions. Main effects were stepped out of the model if the associated p-value was greater than 0.15 and interactions were entered into the model if the associated p-value was less than or equal to 0.05. The alternative strategy was used to avoid overspecification of the model and minimize collinearity among terms that can lead to imprecise parameter and standard error estimates.

TABLE 4-7.

Summary of Statistical Procedures

Chi-square Contingency Table Test

The chi-square test of independence (11) is calculated for a contingency table by the following formula:

$$\chi^2 = \Sigma(f_o - f_e)^2/f_e$$

where the sum is taken over all cells of the contingency table and

f_o = observed frequency in a cell

f_e = expected frequency under the hypothesis of independence.

Large values indicate deviations from the null hypothesis and are tested for significance by comparing the calculated χ^2 to the tables of the chi-square distribution.

Fisher's Exact Test

Fisher's exact test (11) is a randomization test of the hypothesis of independence for a 2 x 2 contingency table. This technique was used for small samples and sparse cells. This is a permutation test based on the exact probability of observing the particular set of frequencies, or of one more extreme.

Correlation Coefficient (Pearson's Product-Moment)

The population correlation coefficient (12), ρ, measures the strength of the linear relationship between two random variables X and Y. A commonly used sample-based estimate of this correlation coefficient is

$$r = \frac{\sum(x_i - \bar{x})(y_i - \bar{y})}{\left[\sum(x_i - \bar{x})^2 \sum(y_i - \bar{y})^2\right]^{1/2}}$$

where the sum is taken over all (x,y) pairs in the sample. A Student's t-test based on this estimator is used to test for a significant correlation between the two random variables of interest. For the sample size of 521 (the size of the Ranch Hand cohort under the minimal assumption), a sample correlation coefficient of ±0.086 is sufficient to attain a statistically significant correlation at a 5 percent level for a two-sided hypothesis test. Assuming normality of X and Y for the sample size of 742 under the maximal assumption, a sample coefficient of ±0.072 is sufficient.

TABLE 4-7. (Continued)

Summary of Statistical Procedures

General Linear Models Analysis

The form of the general linear model (13) for two independent variables is

$$Y = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \varepsilon$$

where

Y = dependent variable (continuous)

α = level of Y at $X_1 = 0$ and $X_2 = 0$, i.e., the intercept

X_1, X_2 = measured value of the first and second independent variables, respectively, which may be continuous or discrete

β_1, β_2 = coefficient indicating linear association between Y and X_1, Y and X_2, respectively; each coefficient reflects the effect on the model of the corresponding independent variable adjusted for the effect of the other independent variable.

β_{12} = coefficient reflecting the linear interaction of X_1 and X_2, adjusted for linear main effects

ε = error term.

This model assumes that the error terms are independent and normally distributed with a mean of 0 and a constant variance. Extension to more than two independent variables and interaction terms is immediate.

Simple linear regression, multiple linear regression, analysis of variance, analysis of covariance, and repeated measures analysis of variance are all examples of general linear models analysis.

Logistic Regression Analysis

The logistic regression model (11, 14) enables a dichotomous dependent variable to be modeled in a regression framework with continuous and/or discrete independent variables. For two risk factors, such as dioxin and age, the logistic regression model would be

$$\text{logit } P = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \varepsilon$$

TABLE 4-7. (Continued)

Summary of Statistical Procedures

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where

P	=	probability of disease for an individual with risk factors X_1 and X_2
logit P	=	ln (P/1-P), i.e., the log odds for disease
X_1	=	first risk factor, e.g., dioxin
X_2	=	second risk factor, e.g., age.

The parameters are interpreted as follows:

α	=	log odds for the disease when $X_1 = 0$ and $X_2 = 0$
β_1	=	coefficient indicating the dioxin effect adjusted for age
β_2	=	coefficient indicating the age effect adjusted for dioxin
β_{12}	=	coefficient indicating the interaction between dioxin and age, adjusted for linear main effects
ε	=	error term.

In the absence of an interaction ($\beta_{12} = 0$) for a dichotomous risk factor (e.g., Comparisons, Ranch Hands), $\exp(\beta_1)$ reflects the adjusted odds ratio for individuals in group 1 ($X_1 = 1$) relative to group 0 ($X_1 = 0$). If the probability of disease is small, the odds ratio will be approximately equal to the relative risk. In the absence of an interaction for a continuous risk factor (e.g., initial dioxin in its continuous form), $\exp(\beta_1)$ reflects the adjusted odds ratio for a unit increase in the risk factor. If the risk factor is expressed in logarithmic (base 2) form, $\exp(\beta_1)$ reflects the adjusted odds ratio for a twofold increase in the risk factor.

Throughout this report, the adjusted odds ratios will be referred to as adjusted relative risks. Correspondingly, in the absence of covariates (i.e., unadjusted analysis), the odds ratios will be referred to as estimated relative risks.

This technique will also be used for longitudinal analyses of dichotomous dependent variables to examine changes in health status between 1982 (or 1985) and 1987 in relation to the dioxin measures.

TABLE 4-7. (Continued)

Summary of Statistical Procedures

Log-linear Analysis

Log-linear analysis (11) is a statistical technique for analyzing cross-classified data or contingency tables. A saturated log-linear model for a three-way table is

$$\ln (Z_{ijk}) = U_o + U_{1(i)} + U_{2(j)} + U_{3(k)} + U_{12(ij)} + U_{23(jk)} + U_{13(ik)} + U_{123(ijk)}$$

where

Z_{ijk} = expected cell count

$U_{1(i)}$ = specific one-factor effect

$U_{12(ij)}$ = specific two-factor effect or interaction

$U_{123(ijk)}$ = three-factor effect or interaction.

The simplest models are obtained by including only the significant U-terms. Adjusted relative risks are derived from the estimated U-terms from an adequately fitting model.

In the analysis of a particular health variable, when no dioxin-by-covariate interactions were significant at the 0.05 level, adjusted means (15) or relative risks were presented. If a dioxin-by-covariate interaction was significant at the 0.05 level, the behavior of the dioxin variable was explored for different levels (categories) of the covariate to identify subpopulations for which a dioxin relationship might exist. Further, for illustrative purposes, if any dioxin-by-covariate interaction was significant at a level between 0.01 and 0.05, the adjusted means or relative risks also were presented, after dropping the interaction terms from the model.

In some instances a followup model also was performed that excluded a highly significant interaction ($p<0.01$). This optional model was run at the discretion of the analyst in an attempt to simplify the interpretation that may be complicated by an interaction difficult to explain from a clinical perspective.

For all models that included a dioxin-by-covariate interaction, the stratified results presented in the appendices display adjusted relative risks, confidence intervals, and associated p-values determined from a model that included the interaction term. However, in the model 2 analyses the p-values for the stratified current dioxin-by-time since tour interaction terms were determined from separate models for each covariate stratum; similarly in the model 3 analyses, the overall p-values were determined from separate models.

The adjusted models assessed the statistical significance of interactions between dioxin and the covariates to determine whether the relationship between dioxin and the dependent variable (health-related endpoint) differed across levels of the covariate. In many instances the clinical importance of a statistically significant dioxin-by-covariate interaction is unknown or uncertain. The clinical relevance of a statistically significant interaction would be strengthened if the same interaction persisted among related endpoints. It is recognized that due to the large number of dioxin-by-covariate interactions that were examined for approximately 300 variables, some of the dioxin-by-covariate interactions judged significant at the 0.05 level might be spurious; i.e., chance occurrences not of biological/clinical relevance. This should be considered when significant dioxin-by-covariate interactions are interpreted. It is important that the size of the p-value associated with each dioxin-by-covariate interaction be weighed carefully; for this reason, if the p-value for a dioxin-by-covariate interaction was between 0.01 and 0.05, the adjusted means or relative risks (omitting the interaction) were reported.

For the neurology, cardiovascular, renal, and endocrine clinical assessments, additional analyses were performed when certain covariates were retained in the final model. These covariates were variables that may have been affected by dioxin exposure and included diabetic class (neurology and renal), percent body fat (cardiovascular and endocrine), and cholesterol (cardiovascular). Due to the association between these covariates and dioxin, both the statistical and clinical interpretation of other health variables can be affected. Analyses were consequently performed with these covariates in the final model, and with the covariates removed from the model. Tabular results with these covariates in the model are given in the body of the clinical chapter; results with these covariates removed are given in the associated chapter appendix.

POWER

Conducting a statistical test using a type I error, also called alpha level, of 0.05 means that, on the average in 5 cases out of 100, a false conclusion would be made that an association (dioxin effect) exists when, in reality, there is no association. The other possible inference error (called a type II error) is the failure to detect an association when one actually exists. The probability of a type II error for a statistical test is 1 minus the power of the test. The power of the test is the probability that the test will reject the hypothesis of no dioxin effect when an effect does in fact exist. The power of a test depends on the distribution of the dioxin data, the sample size, the disease prevalence rate, and the true dioxin effect measured in terms of the relative risk.

Table 4-8 contains the approximate power for detecting specified relative risks for a given prevalence rate (discrete dependent variable), using initial dioxin in its continuous form and an alpha level of 0.05 for a two-sided test under the minimal assumption (n=521). The corresponding power under the maximal assumption is slightly higher. Figure 4-3 presents a graphical display of the power at different prevalence rates, where the different curves represent relative risks of 1.1, 1.2, 1.3, 1.4, and 1.5. Power calculations were performed using the logarithm (base 2) of initial dioxin, and consequently the relative risk is for a twofold increase in initial dioxin. These calculations also assume approximate prevalences at the mean $\log_2$ (initial dioxin) value of 7.49, corresponding to an initial dioxin level of 180 ppt.

TABLE 4-8.

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

Prevalence Rate of Disease	Relative Risk 1.10	1.20	1.30	1.40	1.50	1.75	2.00
0.005	0.05	0.07	0.09	0.12	0.17	0.33	0.54
0.01	0.06	0.09	0.13	0.20	0.29	0.56	0.80
0.02	0.07	0.12	0.21	0.34	0.49	0.82	0.96
0.03	0.08	0.16	0.29	0.46	0.64	0.93	0.99
0.04	0.08	0.19	0.36	0.57	0.75	0.97	1.00
0.05	0.09	0.22	0.43	0.65	0.83	0.99	1.00
0.10	0.13	0.36	0.66	0.88	0.97	1.00	1.00
0.15	0.16	0.47	0.79	0.95	0.99	1.00	1.00
0.20	0.18	0.55	0.86	0.97	1.00	1.00	1.00