

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

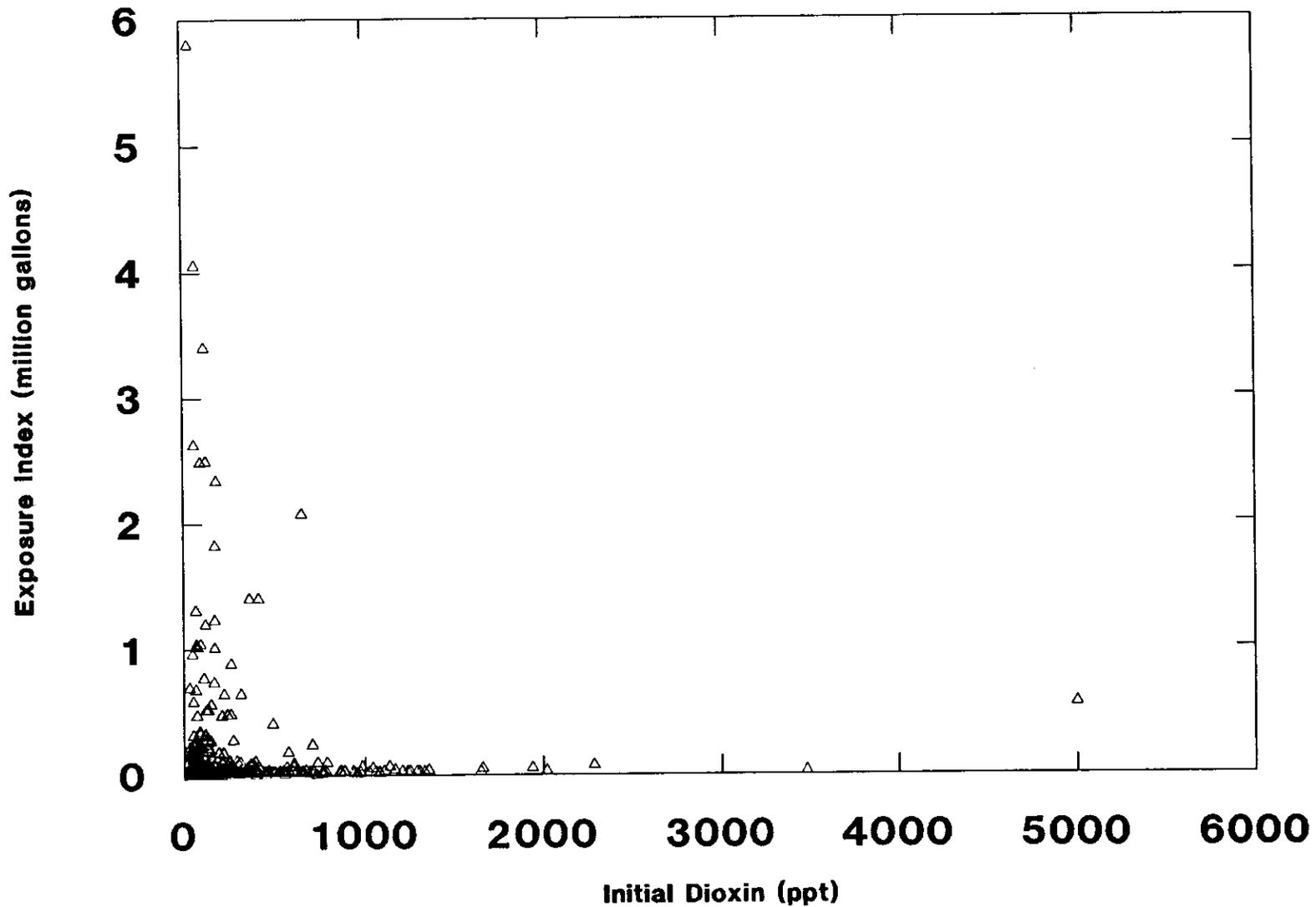


FIGURE 3-1. Initial Dioxin versus the Exposure Index in Ranch Hands With Current Dioxin Greater Than 5 ppt (N=742)

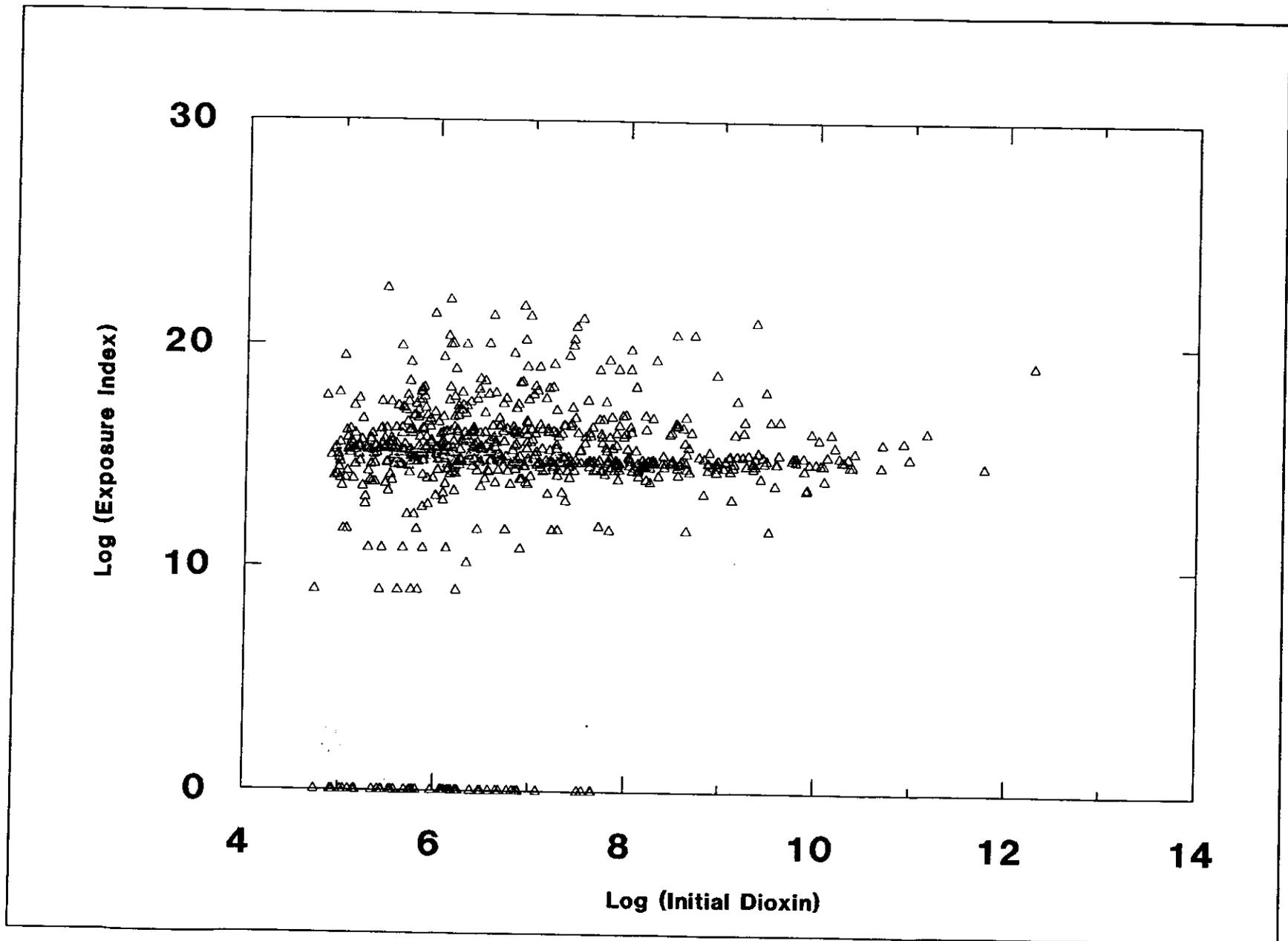


FIGURE 3-2. Logarithm of Initial Dioxin versus Logarithm of the Exposure Index in Ranch Hands With Current Dioxin Greater Than 5 ppt (N=742)

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				Total
	Zero	Low	Medium	High	
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

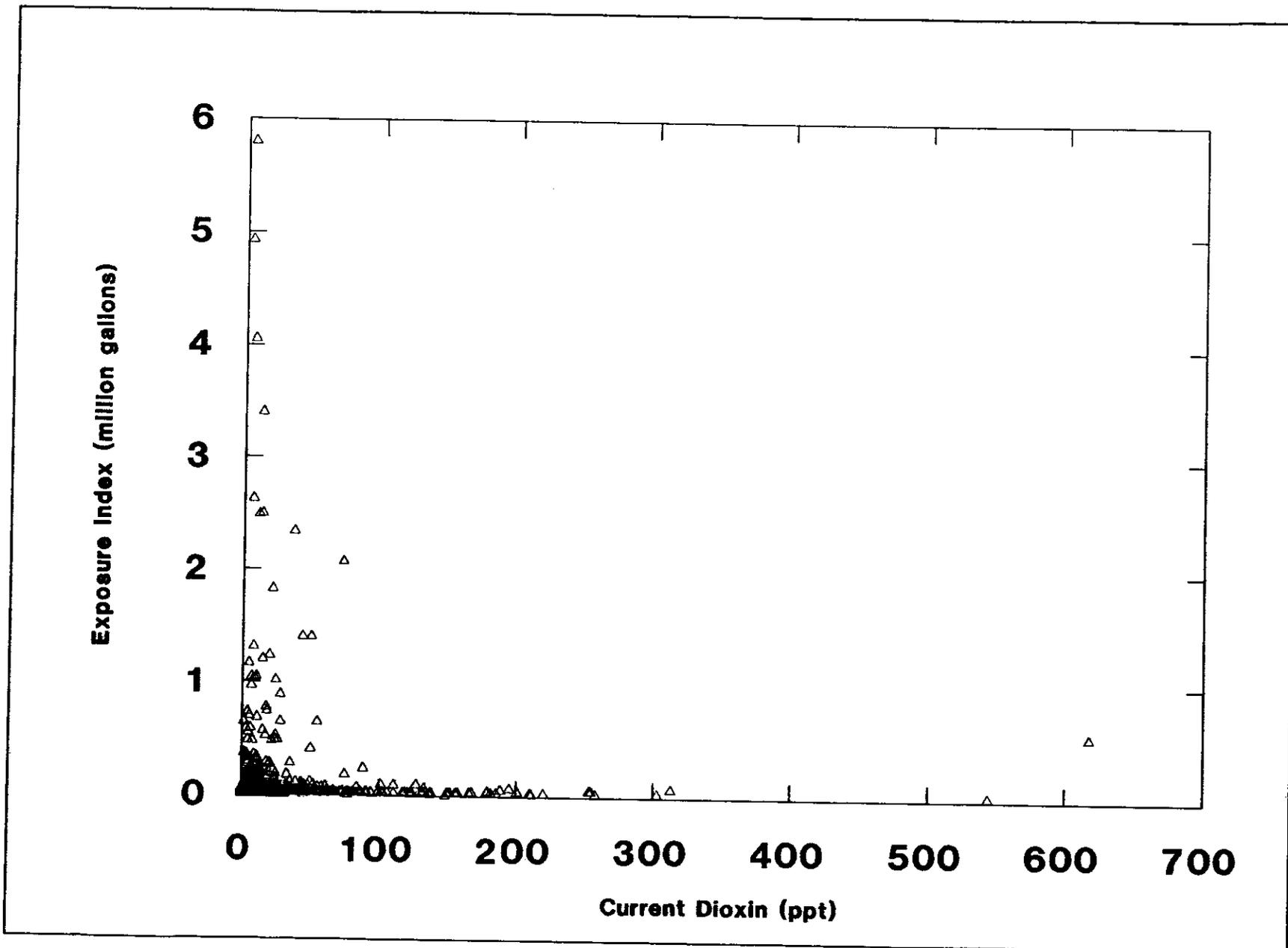


FIGURE 3-3. Current Dioxin versus the Exposure Index in Ranch Hands (N=866)

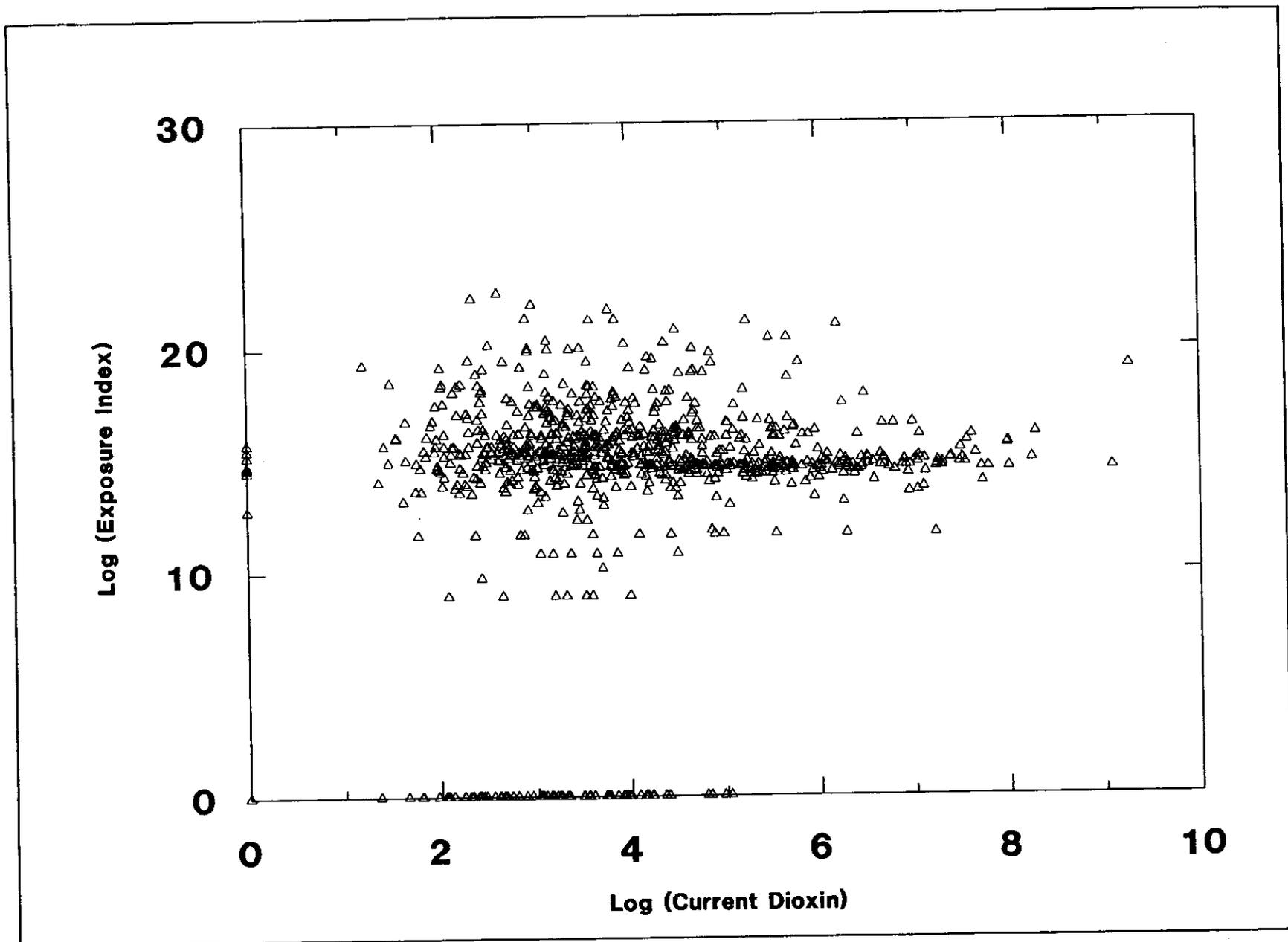


FIGURE 3-4. Logarithm of Current Dioxin versus Logarithm of the Exposure Index in Ranch Hands (N-866)

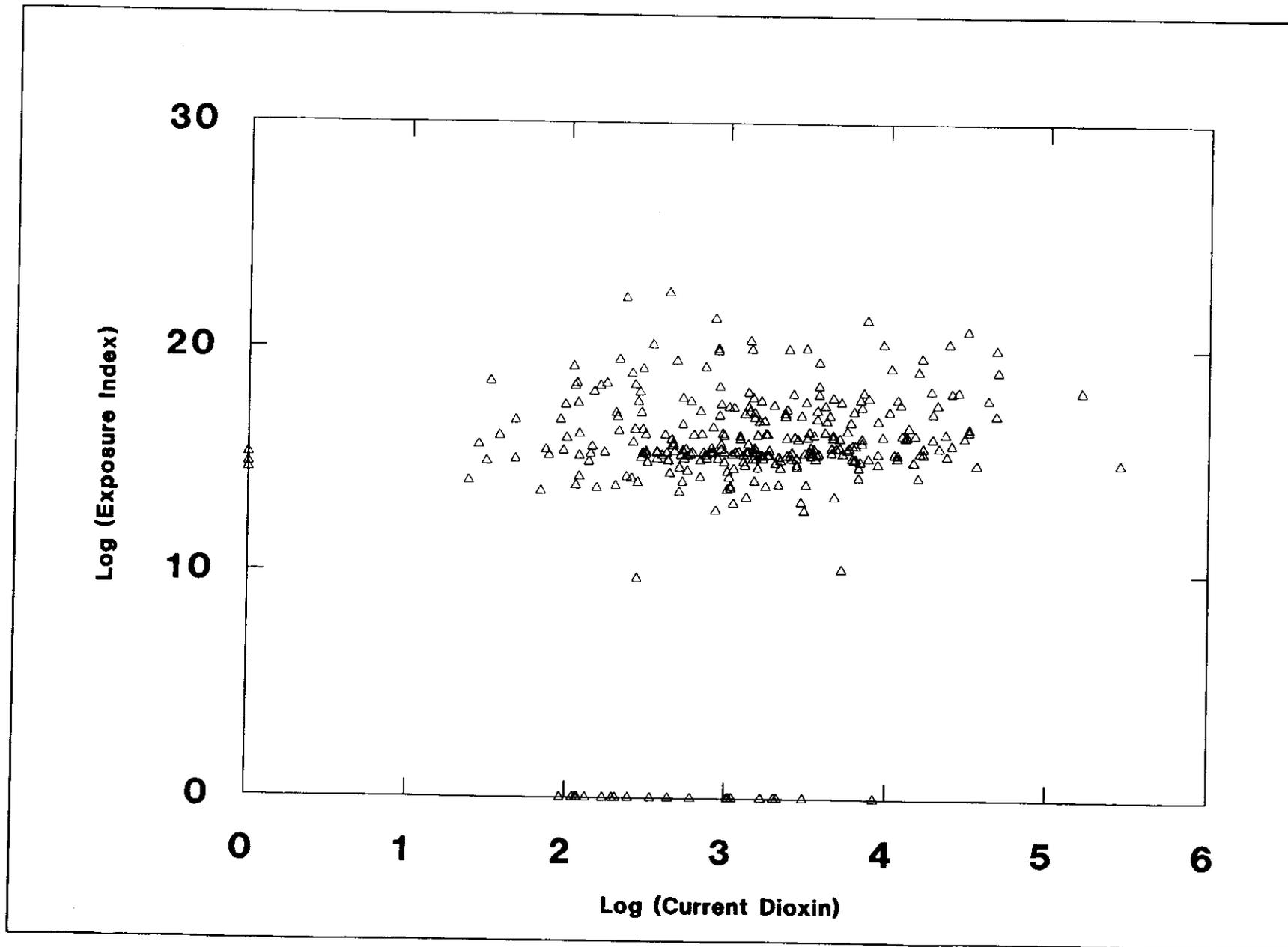


FIGURE 3-5. Logarithm of Current Dioxin versus Logarithm of the Exposure Index in Ranch Hand Officers (N=319)

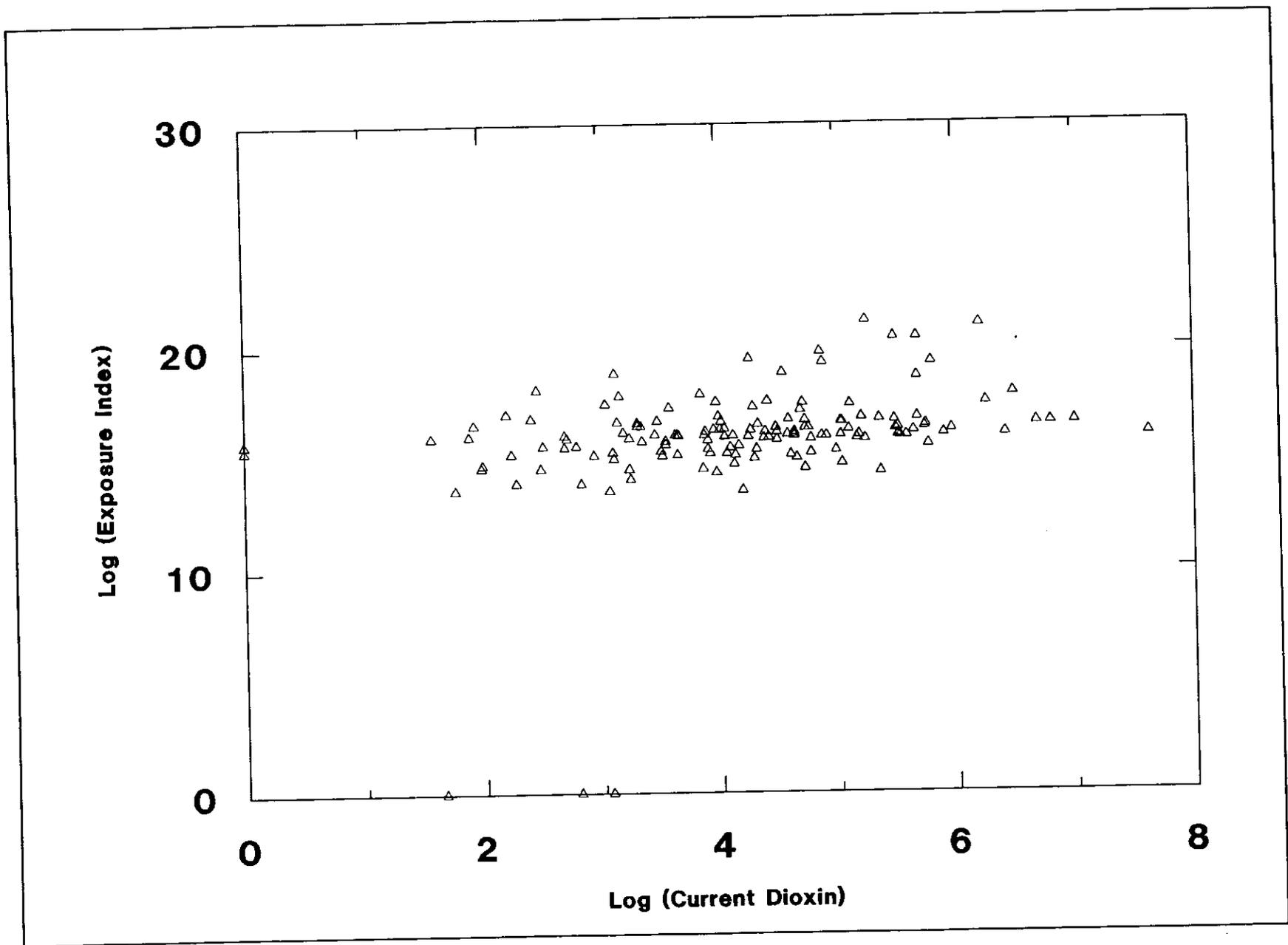


FIGURE 3-6. Logarithm of Current Dioxin versus Logarithm of the Exposure Index in Ranch Hand Enlisted Flyers (N=148)

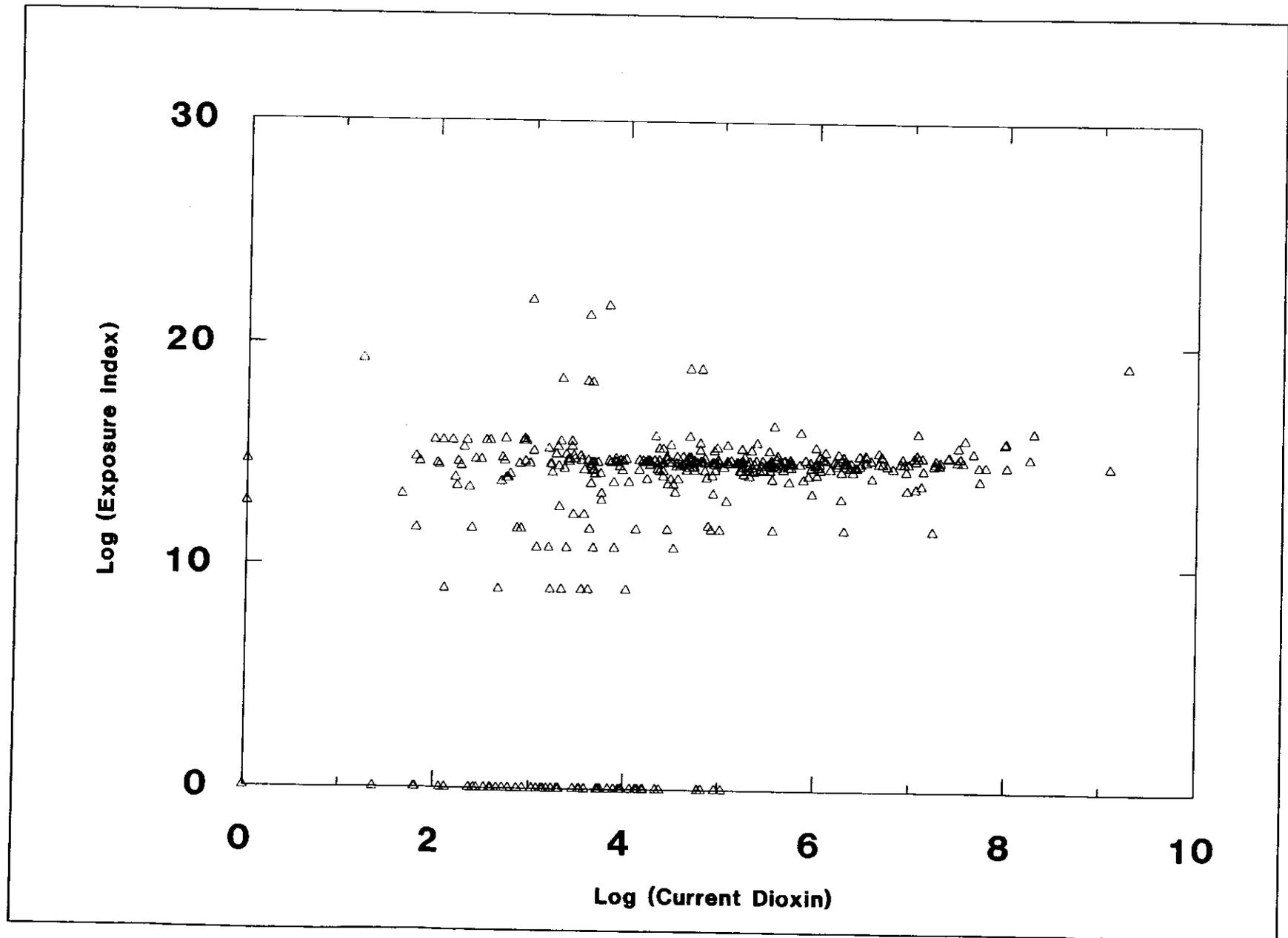


FIGURE 3-7. Logarithm of Current Dioxin versus Logarithm of the Exposure Index in Ranch Hand Enlisted Groundcrew (N=399)

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				Total
		Zero	Low	Medium	High	
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				Total
	Zero	Low	Medium	High	
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				Total
		Zero	Low	Medium	High	
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

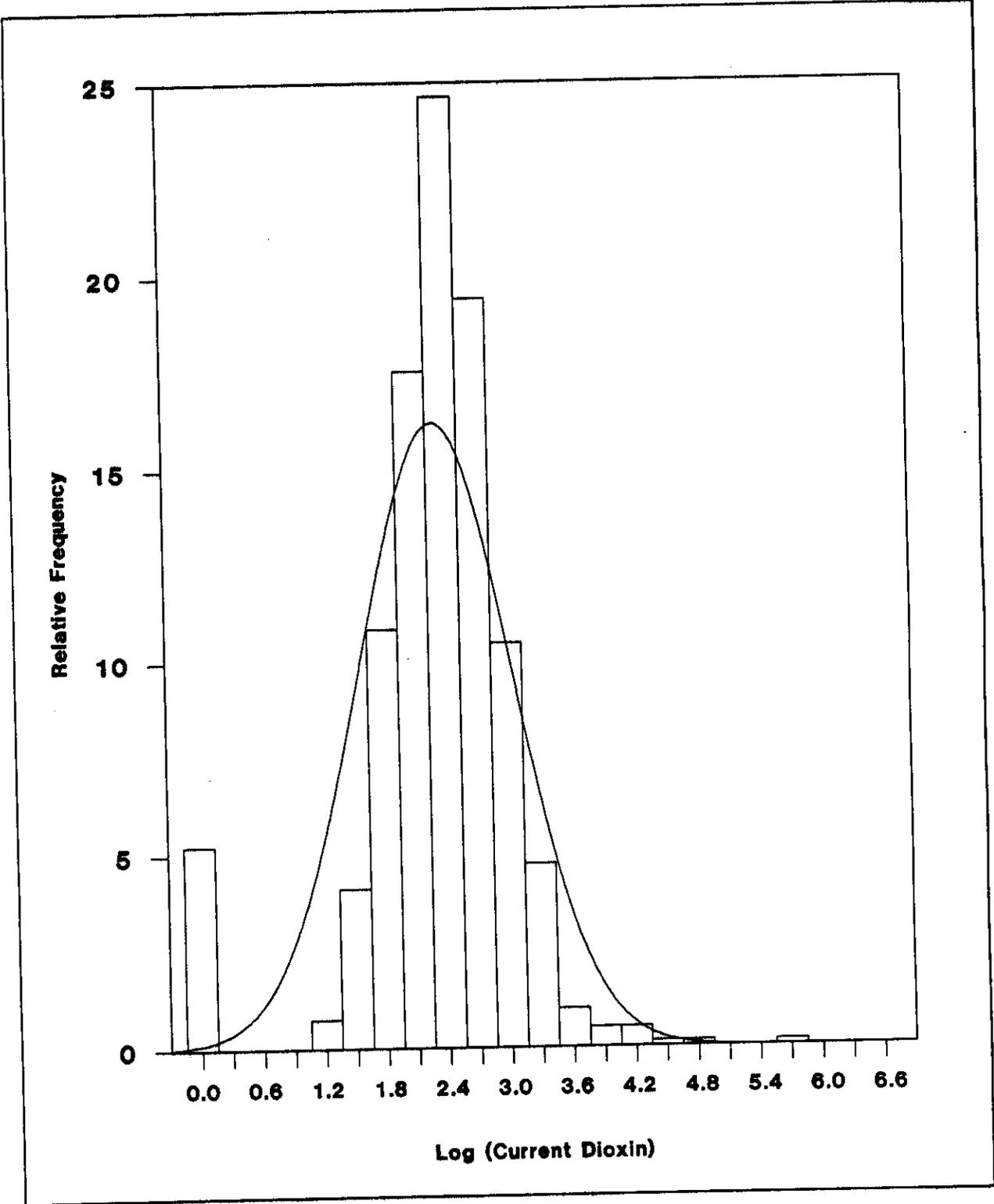


FIGURE 3-8. Relative Frequency Distribution of the Logarithm of Current Dioxin in Comparisons (N=804)

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.

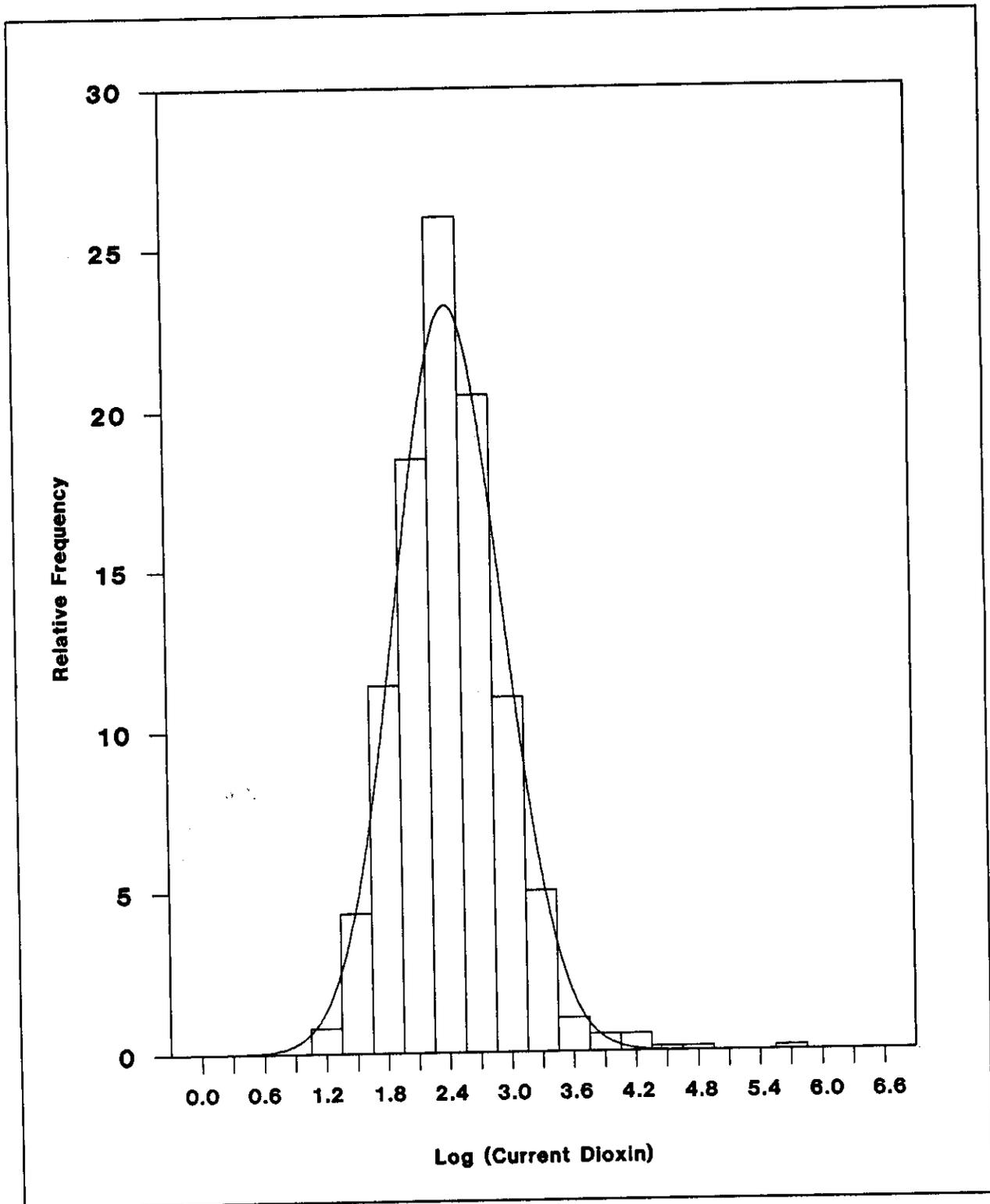


FIGURE 3-9. Relative Frequency Distribution of the Logarithm of Current Dioxin in Comparisons With Current Dioxin Greater Than Zero (N=762)

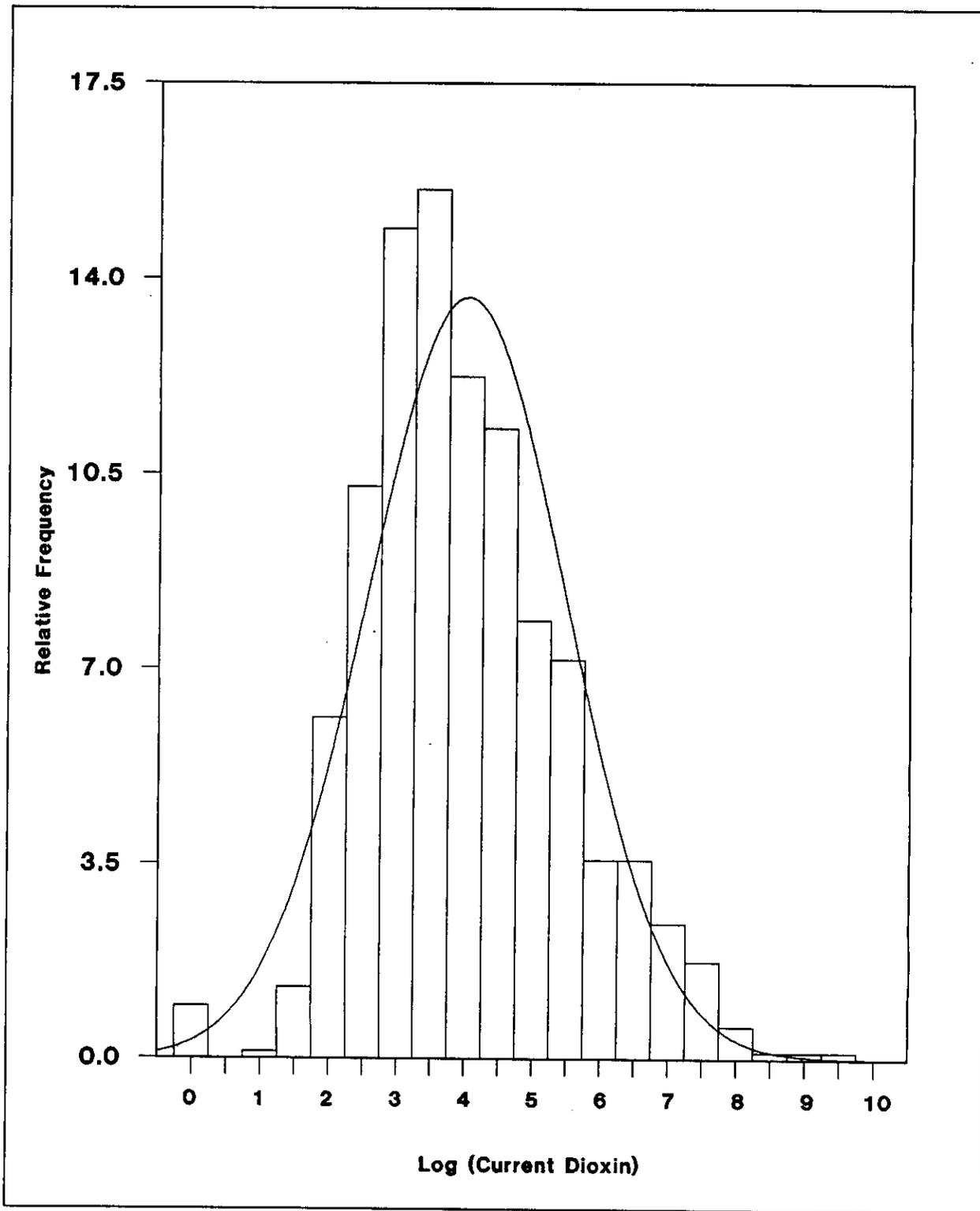


FIGURE 3-10. Relative Frequency Distribution of the Logarithm of Current Dioxin in Ranch Hands (N=866)

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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.