TABLE 12-9. (continued)

Adjusted Exposure Index Analyses for Psychological Variables by Occupation

Variable	Occupation	Statistic*	Exposure Index Low	Medium	High	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
A-H Area Subscore	Officer	n	111	109	112	Overall		0.546
						M vs. L	0.78 (0.44,1.37)	0.383
						H vs. L	0.75 (0.43,1.31)	0.311
	Enlisted Flyer	n	45	57	45	Overall		****(3,4)
						M vs. L	****(3,4)	****(3,4)
						H vs. L	****(3,4)	****(3,4)
	Enlisted Groundcrew	n	129	145	118	Overall		0.427
						M vs. L	0.84 (0.50,1.40)	0.499
						H vs. L	0.92 (0.53,1.59)	0.767
HRB Impairment Index	Officer	n	124	126	118	Overall		0.255
						M vs. L	0.81 (0.43,1.53)	0.512
						H vs. L	0.57 (0.29,1.12)	0.103
	Enlisted Flyer	n	47	61	52	Overall		0.159
						M vs. L	2.28 (0.96,5.44)	0.063
						H vs. L	1.39 (0.58,3.37)	0.461
	Enlisted Groundcrew	n	145	158	127	Overall		****(1)
						M vs. L	****(1)	****(1)
						H vs. L	****(1)	****(1)

TABLE 12-9. (continued)

Adjusted Exposure Index Analyses
for Psychological Variables by Occupation

---

*n: represents total sample size for variable in given occupational stratum.

(a): marginal exposure index by race interaction (p=0.055) -- relative risk, confidence interval, and p-value presented, and additional information provided in interaction summaries.

(b): converted from log (X+1) scale, where X was the number of questions answered yes.

****(1): exposure index-by-race interaction -- relative risk, confidence interval, and p-value not presented.

****(2): exposure index-by-age interaction -- relative risk, confidence interval, and p-value not presented.

****(3): exposure index-by-education interaction -- relative risk, confidence interval, and p-value not presented.

****(4): exposure index-by-drink-year interaction -- relative risk/adjusted mean, confidence interval, and p-value not presented.

****(3,4): exposure index-by-education and exposure index-by-drink-year interaction -- relative risk/adjusted mean, confidence interval, and p-value not presented.

----: no relative risk given for Total CMI, which was analyzed as a continuous variable.

Unadjusted analyses revealed a borderline significant difference between the high and low exposure levels for masculinity/femininity in officers (Est. RR: 2.38, 95% C.I.: [0.94,6.06], p=0.075), and for the total CMI in officers (low mean: 7.99, high mean: 10.04, p=0.018; overall p-value: 0.049). These data supported an increase in the proportion of abnormalities with increasing exposure levels. Other significant or marginally significant results were associated with a decrease in the proportion of abnormalities with an increase in exposure level.

The frequency of abnormalities for the different exposure index levels exhibited no graduated pattern across exposure levels. Within the officer stratum, five variables demonstrated an increasing dose-response relationship, although usually nonsignificant; however, four variables showed the opposite pattern, that is, a decreasing proportion of abnormalities with increasing exposure levels.

Few significant results were observed in the adjusted analysis, as in the unadjusted analysis. The medium level of the HRB impairment index for enlisted flyers showed an increased relative risk over the low level (Adj. RR: 2.28, 95% C.I.: [0.96,5.44], p=0.063). Many exposure index-by-covariate interactions were present, however, which prevented a direct comparison.

Interactions were present for 13 of the 18 variables, but no occupational stratum was predominant. A summary of these interactions is presented in Table 12-10.

TABLE 12-10.

Summary of Exposure Index-by-Covariate Interactions in Adjusted Analyses of Psychological Variables

Variable	Occupation	Covariate	p-Value
Anxiety	Enlisted Groundcrew	Race	0.020
Denial	Officer	Age	0.048
Depression	Enlisted Groundcrew	Race	0.050
Hypochondria	Officer	Education	0.005
Hypochondria	Enlisted Groundcrew	Race	0.033
Hysteria	Officer	Education	0.018
Hysteria	Enlisted Groundcrew	Race	0.007
Mania/Hypomania	Officer	Drink-Years	0.015
Masculinity/Feminity	Officer	Education	0.018
Paranoia	Officer	Age	0.044
Paranoia	Enlisted Flyer	Age	0.004
Paranoia	Enlisted Groundcrew	Race	0.055 (marginal)
Psychopathic/Deviate	Enlisted Groundcrew	Education	0.040
Total CMI	Officer	Drink-Years	0.034
Total CMI	Enlisted Flyer	Education	0.027
Total CMI	Enlisted Flyer	Drink-Years	0.021
M-R Subscore	Enlisted Flyer	Drink-Years	0.042
A-H Area Subscore	Enlisted Flyer	Education	0.009
A-H Area Subscore	Enlisted Flyer	Drink-Years	0.004
HRB Impairment Index	Enlisted Groundcrew	Race	0.031

Significant or borderline significant results in these interactions, suggestive of a dose-response relationship (i.e., increasing abnormalities or more abnormal means as exposure increases), were as follows:

(1) Hysteria in college-educated officers, overall p-value = 0.025; high versus low contrast (Adj. RR: 3.49, 95% C.I.: [1.17,10.32], p=0.024); increase in the proportion of abnormalities with increasing exposure levels.

(2) Mania/Hypomania in officers with greater than 50 drink-years, high versus low contrast, p=0.067; analysis affected by sparse cell sizes, however.

(3) Masculinity/Femininity in college-educated officers, medium versus low contrast (Adj. RR: 3.05, 95% C.I.: [1.01,9.08], p=0.048); increase in the proportion of abnormalities with increasing exposure levels.

(4) Total CMI in high school-educated, nondrinking, enlisted flyers, medium versus low contrast, p=0.018.

(5) Total CMI in college-educated, nondrinking, enlisted flyers, overall p-value =0.060; analysis affected by sparse cell sizes, however.

(6) M-R subscore in nondrinking, enlisted flyers, overall p-value = 0.060; analysis affected by sparse cell sizes, however.

(7) A-H area subscore in high school-educated, nondrinking, enlisted flyers, overall p-value = 0.007; analysis affected by sparse cell sizes, however.

(8) HRB impairment index in nonblack enlisted groundcrew, medium versus low contrast (Adj. RR: 1.88, 95% C.I.: [1.09,3.25], p=0.024).

All other significant interaction results were not consistent with a dose-response relationship.

In summary, no consistent or strong patterns of increasing dose-response relationship were evident throughout the psychological exposure index analyses.

LONGITUDINAL ANALYSES

Two scales for the MMPI, depression and denial, were significantly different by group at Baseline and were investigated to assess the longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. Both variables are scores and were classified as abnormal or normal according to criteria given previously. These variables have been stratified by education level. As shown in Table 12-11, 2x2 tables were constructed for each group for each variable. These tables show the number of participants who were abnormal at Baseline and abnormal at followup, abnormal at Baseline and normal at followup, normal at Baseline and abnormal at followup, and normal at both Baseline and followup examinations.

TABLE 12-11.

Longitudinal Analysis of Depression and Denial:
A Contrast of Baseline and First
Followup Examination Abnormalities

Variable	Education	Group	1982 Baseline Exam	1985 Followup Exam		Odds Ratio (OR)*	p-Value (OR_{RH} vs/OR_C)
				Abnormal	Normal		
Depression	High School	Ranch Hand	Abnormal	59	48	0.65	
			Normal	31	570		0.04
		Comparison	Abnormal	44	43	1.21	
			Normal	52	695		
	College	Ranch Hand	Abnormal	11	9	1.11	
			Normal	10	227		0.73
		Comparison	Abnormal	7	11	1.36	
			Normal	15	276		
Denial	High School	Ranch Hand	Abnormal	2	5	2.20	
			Normal	11	690		0.56
		Comparison	Abnormal	6	10	3.20	
			Normal	32	786		
	College	Ranch Hand	Abnormal	0	3	1.67	
			Normal	5	249		0.32
		Comparison	Abnormal	5	3	4.33	
			Normal	13	288		

*Odds Ratio: $\frac{\text{Number Normal Baseline, Abnormal Followup}}{\text{Number Abnormal Baseline, Normal Followup}}$

The odds ratio given is the ratio of the number of participants who were normal at the Baseline and abnormal at the followup to the number of participants who were abnormal at the Baseline and normal at the followup (the "off-diagonal" elements). The changes in normal/abnormal status within each group are contrasted between the Ranch Hand and Comparison groups, and the p-value is derived from Pearson's chi-square test of the hypothesis that the pattern of change in the two groups is the same.

The data showed a significant difference ($p=0.04$) in the depression scores in the two groups between examinations for the high school-educated stratum: significantly more Comparisons developed depression in the interval. The percentage of Ranch Hands with abnormalities for depression decreased from the Baseline examination to the followup examination, in contrast to the Comparison group, which showed an increase in depression abnormalities. No significant difference in the pattern of change for depression was found in the college-educated stratum, nor were any significant differences observed for denial.

DISCUSSION

The MMPI is a comprehensive, self-administered questionnaire containing 566 questions that broadly assess behavior, personality, and validity and consistency indicators of the responses. The MMPI data are divided into 14 scales that are not mutually exclusive for specific questions. In this study, an additional MMPI scale for the characterization of PTSD is used to identify highly correlated combat experiences of the participants. Four combat questions were selected as a surrogate measure of PTSD, and an index of these questions is used as a covariate in all of the adjusted analyses of the MMPI subscales.

Distributional testing for the 14 scales of the MMPI, stratified by occupation, yielded no significant differences or discernible patterns between the two groups. In contrast, both unadjusted and adjusted analyses showed significant group differences for the denial and masculinity/femininity scales, with the Comparisons having higher proportions of abnormalities than the Ranch Hands. Also, borderline significant associations ($0.05<p\leq 0.10$) were observed for the hysteria and social introversion scales, with the Ranch Hands having slightly higher proportions of abnormalities than the Comparisons. The discrepancy in results between Kolmogorov-Smirnov distributional testing and the refined statistical models was also noted in the 1984 Baseline Report.

The unadjusted and adjusted results were completely comparable with respect to group differences when direct contrast was possible, i.e., when no group-by-covariate interactions were present. Of the seven group interactions noted in the adjusted analyses, three involved the covariate of education, with the high school-educated Ranch Hands faring worse than high school-educated Comparisons. Further, the high school strata usually exhibited a higher frequency of abnormalities than the college-educated strata. Overall education showed a profound effect either as a main effect or by an interaction with another covariate. The strong influence of education was also detected in the Baseline data. Analyses using only the Original Comparisons often showed stronger group differences than the analyses based upon the total Comparison group (see Tables J-13 to J-18 of Appendix J).

A direct comparison of the MMPI results between the Baseline and followup examinations is hampered by the small change in cohorts and the difference in statistical models. In general, at the followup the Ranch Hands manifested more MMPI scale abnormalities than the Comparisons, as judged by the number of relative risks greater than one. However, the highly significant results for the denial scale, with the Comparisons having a higher proportion of abnormalities than the Ranch Hands, suggested that the Comparisons may be underreporting on all of the MMPI scales, and consequently more relative risks greater than one would be expected. A contrast of the adjusted Baseline MMPI results to the adjusted (and unadjusted results where interactions are noted in the adjusted tests) results of the followup suggest a relatively consistent pattern of narrowing group differences over time (e.g., hypochrondria, depression, hysteria, schizophrenia scales), either by a decrease in Ranch Hand abnormalities or an increase of Comparison abnormalities. This trend was also suggested in the longitudinal analysis of two scales (depression and denial) although only the "favorable" Ranch Hand change in depression for the high school stratum reached statistical significance. Overall, the followup MMPI data suggested a subtle, but consistent, decrease in reporting of concerns (or strength of concerns) in the Ranch Hands.

Only 16 participants were identified as possibly having PTSD by the MMPI subscale. Further, only 4 of 15 combat experience questions manifested strong correlation to these possible PTSD cases. Most PTSD surveys have focused on U.S. Army ground personnel, obscuring direct comparisons to U.S. Air Force personnel because of inherent differences in combat experience, education, proportion of officers, and career motivation.

The CMI revealed a significant group difference for the total score and the A-H area subscore, with the Ranch Hands exhibiting higher mean scores or higher frequencies of abnormal scores. There was no group difference for the M-R subscore. These results differed slightly from the distributional tests which showed one statistically significant stratum, where the Ranch Hand mean was greater than the Comparison mean, for each covariate (see Table J-5 of Appendix J). Because the Baseline CMI was in a different format, direct comparison of each psychological parameter to the followup CMI is not feasible. However, the Baseline CMI noted statistically significant group differences for 5 of 10 parameters, which is in approximate accord with the magnitude and direction of the results found at the followup examination. This analysis of the total CMI analyzed at followup has sufficient statistical power to detect a mean difference of one response out of 195 questions (0.5% difference, at power=0.8) between the groups. Education showed the same profound effect on the adjusted analyses as was noted at Baseline.

The functional integrity of the CNS, as measured by the HRB impairment index, showed no significant group differences. There was similarity (Adj. RR: 1.04, 95% C.I.: [0.86,1.25], p=0.697) in results of the impairment index. As in the Baseline analysis, education was a major covariate in the followup examination; the additionally strong effects of age and race were also noted at the followup examination. Although valid differences exist between groups for some measures, there is no indication that these differences are manifest or confirmed by impaired CNS function, a reasonable medical expectation for chemically induced neurobahavioral pathology. Adjustment of the HRB results for PTSD (not feasible at the Baseline analysis) suggests that some group differences lack organic basis.

SUMMARY AND CONCLUSIONS

Questionnaire data (verified by medical record reviews) for the lifetime events of psychotic illness, alcohol dependence, anxiety, or other neuroses disclosed no significant differences between groups for these conditions.

Analyses of the followup psychological examination emphasized 14 scales from the Minnesota Multiphasic Personality Inventory (MMPI), 3 parameters of the Cornell Medical Index (CMI), and the Halstead-Reitan Battery (HRB) impairment index.

The similarity of the group distribution for the 14 MMPI variables, each stratified by the 3 occupational categories, was examined, and only 2 of the 42 tests approached statistical significance. The group distributions of the total CMI score were similarly contrasted, with separate analyses performed with stratification by the five covariates of age, race, occupation, education, and current drinking status. For one stratum of each of these covariates, a significant difference in the distribution of the Ranch Hand and Comparison scores was found. In all cases for the CMI, the Ranch Hand mean was greater than the Comparison mean. Distributional analyses using Original Comparisons generally reflected the same results as those involving the total Comparison group.

Results of unadjusted and adjusted analyses on all of the 18 psychological variables are given in Table 12-12.

The unadjusted analyses showed a significant difference for the MMPI scales of denial ($p<0.001$) and masculinity/femininity ($p=0.017$), the total CMI ($p<0.001$), and the Section A-H area subscore ($p=0.003$). A borderline significant difference was observed for the MMPI scales of hysteria ($p=0.067$) and social introversion ($p=0.069$). Comparisons had a greater percentage of abnormal scores for the denial and masculinity/femininity scales, whereas Ranch Hands showed adverse findings for the other four variables. The overall MMPI results have been interpreted in light of the significant increased denial in the Comparison group.

The covariates age, education, drink-years, current alcohol use, and occupation had pronounced effects on the psychological variables, with a significant association or a borderline significant association with at least two-thirds of the 18 psychological variables. Many dependent variables in this chapter were affected by age in an expected pattern. Very few variables exhibited this pattern of consistency with drink-years. The intermediate category of greater than 0 to 50 drink-years often had the smallest proportion of abnormalities. The post-traumatic stress disorder (PTSD) variable, derived from a subset of the MMPI, was strongly associated with the CMI measures, but not with the HRB Impairment Index. Race and the Vietnam combat index (used for the MMPI subscales) had significant associations with a lesser amount of the psychological variables (6 of 18 variables and 3 of 14 variables, for race and combat index, respectively).

The adjusted analyses were generally quite similar to the unadjusted analyses with respect to group differences, although a direct comparison of these analyses was often clouded by the presence of a substantial number of interactions (six group-by-covariate interactions were significant, and three interactions approached significance [$0.05<p\leq0.10$]). The MMPI scales of denial and masculinity/femininity were statistically significant in both the

TABLE 12-12.

Overall Summary Results of Adjusted and Unadjusted Analyses of Psychological Variables

Variable	Unadjusted	Adjusted	Direction of Results[a]
Questionnaire:			
Psychological Illness	NS	--	
Psychological Examination:			
MMPI			
Anxiety	NS	NS	
Consistency	NS	****	
Defensiveness	NS	NS	
Denial	<0.001	<0.001	C>RH
Depression	NS	NS	
Hypochondria	NS	NS	
Hysteria	NS*[b]	NS*[b]	RH>C
Mania/Hypomania	NS	NS	
Masculinity/Femininity	0.017	0.020	C>RH
Paranoia	NS	****	
Psychopathic/Deviate	NS	NS	
Schizophrenia	NS	****	
Social Introversion	NS*[b]	****	RH>C
Validity	NS	****	
CMI			
Total CMI	<0.001	****	RH>C
M-R Subscore	NS	NS	
A-H Area Subscore	0.003	0.040	RH>C
HRB			
Impairment Index	NS	NS	

[a]RH>C - more abnormalities in Ranch Hands; C>RH - more abnormalities in Comparisons.

[b]Illnesses include psychosis, alcohol dependence, anxiety, and other neuroses.

--Analysis not performed.

NS: Not significant.

NS*: Borderline significant ($0.05 < p \leq 0.10$).

****Interaction involving group.

adjusted and unadjusted analyses, where Comparisons showed an adverse effect over Ranch Hands. The A-H area subscore of the CMI (suggesting diffuse medical problems) was also significant, where the Ranch Hands had higher mean scores than the Comparisons, suggesting the Ranch Hands had more illness. Education was often involved in significant group interactions with high school-educated Ranch Hands demonstrating a higher percentage of abnormal scores than high school-educated Comparisons. No group differences were observed in the college-educated stratum. The M-R subscore of the CMI, a broad indicator of emotional health, was not statistically different between the two groups.

The HRB impairment index, a measure of central nervous system (CNS) functional integrity, did not differ significantly between the Ranch Hand and Comparison groups. Strong covariates in the adjusted analysis were age, race, and education.

Because of alternate statistical models and slightly different psychological testing parameters, a direct contrast between the psychological results of the Baseline and followup examinations was not always possible. However, several broad patterns were observed: (1) the discordance between distributional tests and results from traditional statistical models of the MMPI variables was noted with data from both examinations; (2) there was a narrowing of group differences at the followup examination for most subjective variables, either by a decrease in Ranch Hand reporting, or by an increase in Comparison reporting; and (3) as at the Baseline, functional CNS testing, as measured by the HRB impairment index, showed no group differences, and did not support an organic basis for differences in self-reported symptomatology. The longitudinal analysis of two MMPI scales, depression and denial, showed a significant reversal of depression seen at Baseline in the high school-educated Ranch Hands.

The determination of PTSD in both Air Force cohorts by a relatively new MMPI scale showed a prevalence rate of less than 1 percent. This low rate is strongly influenced by characteristics of the study population (e.g., age, education, and officer ratio).

Unadjusted exposure index analyses did not reveal any patterns consistent with a dose-response relationship. For the adjusted exposure analyses, approximately one-third presented exposure interactions with the covariates of race, education, and age, but no consistent pattern could be identified.

In conclusion, some test measures of psychological health (MMPI and CMI) did not show substantial adverse effects for either group. Significant test results were present in both groups or were noted in specific subgroups of a covariate. Educational level, age, and alcohol use showed strong effects on the psychological scales and scores in this psychological assessment. There was a subtle but consistent trend for more favorable subjective test results at the followup examination for the Ranch Hands relative to the Comparisons. Testing of the CNS by the HRB demonstrated an almost identical prevalence of pathology in both groups.

CHAPTER 12

REFERENCES

1. Peterson, R.E., M.D. Seefeld, B.J. Christian, C.L. Potter, C.K. Kelling, and R.E. Keesey. 1984. The wasting syndrome in 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity: Basic features and their interpretation. In Banbury report 18: Biological mechanisms of dioxin action, ed. A. Poland and R.D. Kimbrough, pp. 291-308. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory,

2. Dougherty, J.A., G.E. Schulze, R.T. Taylor, and J. Blake. 1984. Behavioral toxicity of an agent orange component: 2,4-D. Oral presentation to the Veterans Administration Advisory Committee on Health-Related Effects of Herbicides, Washington, D.C., December 11, 1984.

3. Ashe, W.F., and R.R. Suskind. 1949, 1950. Reports on chloracne cases, Monsanto Chemical Company, Nitro, West Virginia. In Report of the Kettering Laboratory, December 1949 and April 1950.

4. Suskind, R.R. July 1953. A clinical and environmental survey, Monsanto Chemical Company, Nitro, West Virginia. In Report of the Kettering Laboratory, July 1953.

5. Moses, M., R. Lilis, K.D. Crow, J. Thornton, A. Fischbein, H.A. Anderson, and I.J. Selikoff. 1984. Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichloro-phenoxyacetic acid: Comparison of findings with and without chloracne. Am. J. Ind. Med. 5:161-182.

6. Suskind, R.R., and V.S. Hertzberg. 1984. Human health effects of 2,4,5-T and its toxic contaminants. JAMA 251:2372-2380.

7. Baader, E.W., and A.J. Bauer. 1951. Industrial intoxication due to pentachlorophenol. Ind. Med. Surg. 20:289-290.

8. Suskind, R.R. 1977. Chloracne and associated health problems in the manufacture of 2,4,5-T. Report to the Joint Conference, National Institute of Environmental Health Sciences and International Agency for Research on Cancer, World Health Organization, Lyon, France, January 1977.

9. Goldman, P.J. 1973. Schweist akute Chlorakne, eine Massenintoxikation durch 2,3,7,8-Tetrachlorodibenzodioxin (Severe, acute chloracne, a mass intoxication due to 2,3,7,8-tetrachloridbenzo-dioxin). Der Hautarzt. 24(4):149-152.

10. Vos, J.G., T.J. Sterringa, D. Zellenrath, H.J. Docter, and L.M. Daldkerup. 1977. TCDD accident at a chemical factory in the Netherlands. Report to the Joint Conference, National Institute of Environmental Health Sciences and International Agency for Research on Cancer, World Health Organization, Lyon, France, January 1977.

11. Telegina, K.A., and L.J. Bikbulatova. 1970. Affection of the follicular apparatus of the skin in workers employed in the production of the butyl ester of 2,4,5-T. Vestnik. Derm. Ven. 44:35-39.

12. Jirasek, L., J. Kalensky, K. Kubec, et al. 1974. Acne chlorina, porphyria cutanea tarda and other manifestations of general intoxication during the manufacture of herbicides, part 2. Czech. Dermatol. 49(3):145-157.

13. Pazderova-Vejlupkova, J., M. Nemcova, J. Pickova, L. Jirasek, and E. Lukas. 1981. The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-dioxin in men. Arch. Environ. Health 36:5-11.

14. Poland, A.P., D. Smith, G. Metter, and P. Possick. 1971. A health survey of workers in a 2,4-D and 2,4,5-T plant, with special attention to chloracne, porphyria cutanea tardas, and psychologic parameters. Arch. Environ. Health 22(3):316-327.

15. Oliver, R.M. 1975. Toxic effects of 2,3,7,8-tetrachloro-dibenzo-1, 4-dioxin in laboratory workers. Br. J. Ind. Med. 32:46-53.

16. Hoffman, R.E., P.A. Stehr-Green, K.B. Webb, G. Evans, A.P. Knutsen, W.F. Schramm, J.L. Staake, B.B. Gibson, and K.K. Steinberg. 1986. Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. JAMA 255:2031-2038.

17. Flicker, M.R., and A.L. Young. 1983. Evaluation of veterans for agent orange exposure. Presented at the Symposium on Chlorinated Dioxins and Dibenzofurans in the Total Environment, given before the Division of Environmental Chemistry, American Chemical Society, Washington, D.C, September 1983.

18. Blackburn, A.B. 1983. Review of the effects of agent orange: A psychiatric perspective on the controversy. Military Med. 148:333-340.

19. Diagnostic and statistical manual of mental disorders, 3rd. ed. 1980. Washington, D.C.: American Psychiatry Association.

20. Faltus, F.J., A.D. Sirota, J. Parsons, M. Daamen, and M.L. Schare. 1986. Exacerbation of post-traumatic stress disorder symptomatology in Vietnam veterans. Military Med. 151:648-649.

21. Van Putten, T., and J. Yager. 1984. Posttraumatic stress disorder. Arch. Gen. Psychiatry 41:411-413.

22. Atkinson, R.M., R.G. Henderson, L.F. Sparr, and S. Deale. 1982. Assessment of Vietnam veterans for posttraumatic stress disorder in veterans disability claims. Am. J. Psychiatry 129:1118-1121.

23. Borus, J.F. 1974. Incidence of maladjustment in Vietnam returnees. Arch. Gen. Psychiatry 30:554-557.

24. Keane, T.M., R.F. Malloy, and J.A. Fairbank. 1984. Empirical development of an MMPI subscale for the assessment of combat-related posttraumatic stress disorder. J. Consulting and Clinical Psychology 52:888-891.

25. Yager, T., R. Laufer, and M. Gallops. 1984. Some problems associated with war experience in men of the Vietnam generation. Arch. Gen. Psychiatry 41:327-333.

26. Laufer, R.S., M.S. Gallops, and E. Frey-Wouters. 1984. War stress and trauma: The Vietnam veteran experience. J. Health and Social Behavior 25:65-85.

27. Sierles, F.S., J.J. Chen, R.E. McFarland, and M.A. Taylor. 1983. Post-traumatic stress disorder and concurrent psychiatric illness: A preliminary report. Am. J. Psychiatry 140:1177-1179.

28. Robins, L.N., J.E. Helzer, K.S. Ratcliff, and W. Seyfried. 1982. Validity of the diagnostic interview schedule, version II: DSM-III diagnoses. Psychol. Med. 12:1855-1870.

29. Cornell University Medical College. 1949. Cornell medical index health questionnaire. Ithaca, New York: Cornell University.

CHAPTER 13

GASTROINTESTINAL ASSESSMENT

INTRODUCTION

This system assessment centers on reported peptic ulcer and liver disease, and current hepatic function and porphyria as determined by comprehensive laboratory testing. The liver is a major target organ for single high-dose and continued low-dose exposure to chlorophenols and TCDD. Peptic/stomach ulcer disease and porphyria cutanea tarda (PCT) are suspected clinical endpoints following moderate- to high-level exposures.

A variety of experimental animal studies[1-5] have demonstrated hepatic dysfunction and porphyria following a wide range of exposures to TCDD. The effects of exposure, as measured by enzymatic change, however, generally appear to be more related to species than to dose and route of administration.

Gross organ pathology in the digestive system and associated clinical symptoms have been observed following TCDD oral administration to (or accidental ingestion by) animals. Pathological lesions have included gastric ulcers, metaplasia of the gastric mucosa, ileitus, hepatic hypertrophy and degeneration, hepatic parenchymal cell necrosis, and hepatic lipid accumulation.

Scientific interest has centered on changes in hepatic enzymes following TCDD administration. Clearly, TCDD has proved to be an exceptional inducer of hepatic enzymes and mixed function oxidases, and a powerful inhibitor of other enzymes. Specifically, the induction of cytochrome P-450, a ferrocytochrome enzyme, by TCDD has been demonstrated in many species and most of their tissues. Further, marked increases in cytochrome P-450 have been implicated in the mechanism of hepatotoxicity, although other factors, such as genetic susceptibility via the Ah locus, iron levels, and lipid peroxidation (but not vitamin A), are also contributory.[6-8]

TCDD has also been shown to produce hepatic porphyria in animals by a reduction in uroporphyrinogen decarboxylase, possibly due to the activation of the P-450 enzyme.[9,10] The porphyriogenic effect of TCDD has also been influenced by genetic susceptibility, iron levels, sex, and ambient temperature.[11,12] In correlation with some human studies, hexachlorobenzene was found to be more porphyriogenic than TCDD.[11]

Numerous morbidity studies, predominantly from the industrial sector, have noted significant abnormal liver function in exposed workers, with and without the presence of clinical hepatic disease. Abnormal liver function test results have been found for direct bilirubin, alkaline phosphatase, triglycerides, cholesterol, serum glutamic-oxaloacetic transaminase (SGOT), gamma-glutamyl transpeptidase (GGTP), urine d-glucaric acid, etc.[13-26] The consistent finding of elevated cholesterol levels may have predictive significance with respect to future heart disease (see Chapter 15), but at present there is no evidence for this.

Contemporary studies have focused on two indirect measures of hepatic microsomal activity, GGTP and urine d-glucaric acid. In the study of the English industrial incident, several Seveso investigations, and the two studies of the Monsanto plant in Nitro, West Virginia, there was modest agreement in observing elevated GGTP and urine d-glucaric acid levels in exposed individuals.[18,19,21,22] Common to all studies was the observation that individuals with chloracne manifested significantly more abnormal liver function tests than exposed individuals without chloracne or unexposed individuals, suggesting a link to TCDD exposure.

Several industrial studies have shown altered porphyrin excretion patterns (predominantly an increase in uroporphyrin) or clinical evidence of PCT, particularly in chronically exposed workers.[27-29] Individuals with low chronic exposure or high acute exposure (Seveso) have not shown these signs. Further, detailed reviews of the suspected association have identified the following scientific study design and interpretive problems: (1) multiple etiologies of PCT or abnormal porphyrin excretion patterns (chemical exposure, genetic makeup, alcohol consumption), (2) misdiagnosis of PCT, and (3) confounding of chemical exposures for the industrial cohorts.

Some investigators believe that the PCT cases found in the early U.S. and European studies were more likely caused by exposure to chlorobenzenes than to TCDD.[30] Overall, the evidence at present is inconclusive to establish a causal association between PCT and TCDD exposure.

A recent industrial study based on questionnaire data has suggested an association of stomach/peptic ulcers with exposure to TCDD.[22] This finding at the Monsanto plant differs from similar research using a slightly different cohort at the same plant which produced a negative conclusion on peptic ulcer disease.[31] The gastric ulcer-TCDD association has not been reported in other cohort dioxin morbidity studies, but ulcer disease has generally not been a major research focus. The preliminary gastric ulcer-TCDD association is fortified somewhat by studies that have shown significant gastric mucosal damage in monkeys following oral administration of TCDD.[2]

Baseline Summary Results

The 1982 AFHS examination conducted an extensive evaluation of hepatic status by questionnaire, physical examination, and laboratory testing. The questionnaire elicited data on liver conditions, liver disease, and symptoms compatible with PCT, as well as detailed information on PCT risk factors (e.g., alcohol consumption, chemical exposures). The physical examination measured hepatomegaly when present and determined liver function and porphyrin patterns by a comprehensive battery of 12 laboratory tests.

The questionnaire showed that Ranch Hands reported more miscellaneous liver conditions (verified by medical record reviews) and more skin changes compatible with PCT than their Comparisons. Although the PCT-reported data were statistically significant, no cases of PCT were diagnosed at examination in either cohort.

The physical examination detected a twofold increase in hepatomegaly in the Ranch Hands, but the numbers were small and not statistically significant. Many of the laboratory test results demonstrated statistical interactions with the covariates. These interactions can be interpreted as being

suggestive of an herbicide effect. Ranch Hands had slightly higher GGTP and lactic dehydrogenase (LDH) results and lower cholesterol levels; no differences were found for bilirubin or alkaline phosphatase levels.

SGOT, serum glutamic-pyruvic transaminase (SGPT), and LDH results in the Ranch Hands interacted with the covariates alcohol, degreasing chemicals, and industrial chemicals differently than they did in the Comparisons. All of these two-factor interactions were statistically significant ($p<0.05$). There were no significant group differences in uroporphyrin, coproporphyrin, or d-aminolevulinic acid levels, nor did any test set support a diagnosis of PCT. Exposure analyses were essentially negative.

The comprehensive hepatic evaluation did not reveal any consistent pattern of significant liver damage in the Ranch Hand group. Nevertheless, because of subtle profile differences in conjunction with questionnaire results and recent literature citations, the gastrointestinal system continues to be targeted for intensive examination throughout all phases of the followup effort.

Parameters of the 1985 Gastrointestinal Assessment

The 1985 AFHS examination continued the emphasis on hepatic function and expanded the porphyrin test battery to six assays. In addition, new components were added to the questionnaire to assess past and current diagnosed peptic ulcer disease, along with a series of screening questions to assess possible undiagnosed disease. Covariate data on aspirin usage, blood group, and family history of peptic ulcer were likewise obtained. Additional probes on intestinal parasites, gallbladder disease, and other liver conditions were also added. Because of the known profound effects of alcohol ingestion on hepatic function, a detailed alcohol consumption history was obtained by questionnaire.

Thus, the dependent variables and covariates in the analyses below reflect a substantial enhancement over those assessed in the 1982 Baseline examination. Because of the effects of increased body temperature and past/current hepatitis B on some liver function tests, participants with a fever of 100 or more degrees Fahrenheit and/or a positive hepatitis B surface antigen (HB_sAg) test were excluded from the analyses. Categorization of continuous clinical variables to dichotomous variables was largely accomplished by use of normal test values from the SCRF laboratory. Minor numeric differences in the tables that follow are due to an occasionally missing value.

The analyses are generally based on 1,009 Ranch Hands and 1,289 total Comparisons after removal of the febrile and positive HB_sAg participants. The statistical analyses relied largely on general linear models (SAS®-GLM), logistic regression techniques (BMDP®-LR), and log-linear models (BMDP®-4F). Parallel analyses using Original Comparisons are found in Tables K-7 to K-16 of Appendix K.

RESULTS AND DISCUSSION

This chapter, entitled "Evaluation of Hepatic Status" in the Baseline Report, incorporates the new elements of peptic ulcer disease and mortality from diseases of the digestive system; hence, the chapter name change to "Gastrointestinal Assessment."

Because of the importance of gastrointestinal disorders, numerous historical and laboratory variables were chosen for evaluation. The analyses are reported in the following order: questionnaire data, mortality data, physical examination findings, laboratory results, exposure index analyses, and representative longitudinal analyses.

Questionnaire Data: Liver Disorders

At the followup examination, each participant was asked whether he had developed hepatitis, jaundice, cirrhosis, or other liver disorders during the interval 1982 to 1985. Affirmative responses were subsequently subject to verification by medical record reviews.

Since the Baseline interview, eight Ranch Hands and five Comparisons cited a verified history of hepatitis ($p=0.264$); four Ranch Hands and five Comparisons reported a subsequently verified history of enlarged liver ($p=0.999$); one from each group noted a verified symptom of jaundice; one Ranch Hand cited a confirmed interval history of cirrhosis; and six Ranch Hands and six Comparisons gave verified histories of seven miscellaneous liver disorders ($p=0.774$). Table 13-1 presents the ICD code and descriptive diagnosis of the miscellaneous liver disorders by group.

Because the number of respondents with new liver disorders was small and precluded meaningful analyses, the verified interval history was added to the verified Baseline history to assess possible lifetime differences for liver disease. These combined results are presented in Table 13-2.

On the basis of combined data, the verified questionnaire responses for historic hepatitis, jaundice, cirrhosis, enlarged liver, and miscellaneous liver disorders did not vary significantly between the Ranch Hand and Comparison groups. The results for miscellaneous liver disorders differed from the Baseline findings. At Baseline, significantly more Ranch Hands than Original Comparisons had a verified liver disorder other than jaundice, hepatitis, or cirrhosis (13/1,045 versus 1/773; $p=0.006$). Subsequent to Baseline, the status of one additional Ranch Hand disorder and one more Original Comparison disorder was verified. Including these two new verified conditions with the data from replacement and shifted Comparisons, the group contrast at Baseline would have been of borderline significance (14/1,045 versus 7/1,224; $p=0.077$). Combining these Baseline data with the followup data resulted in nonsignificant lifetime results. However, the combined Baseline and interval analysis contrasting the Ranch Hands and the Original Comparisons was marginally significant ($p=0.065$) due to the contribution of the significant Baseline results.

The verification status of reported liver symptoms and diseases is presented in Table 13-3. The data reflect the proportions of historic reporting that were verified by medical record reviews, and are contrasted by group for each variable. These data showed that the proportion of verified disease was not statistically significant between groups except for the category of enlarged liver which showed a higher confirmation rate in the Comparison group. Thus, over-reporting or symptom/disease misclassification by the participants was not a function of group membership.

TABLE 13-1.

Number of Other Liver Conditions Reported by Study Participants at Followup by Group (Verified by Medical Record Review)

ICD* Code (Meaning)	Group	
	Ranch Hand	Comparison
5713 (Alcoholic Liver Damage)	1	1
57420 (Calculus of Gallbladder without Mention of Cholecystitis)	0	1
7891 (Hepatomegaly)	1	1
7904/7905 (Enzyme Elevation)	3	0
7948 (Abnormal Liver Scan)	1	1
E9426 (Adverse Effect of Drug)	0	1
M81406 (Adenocarcinoma)	0	1
Total	6	6

*ICD = International Classification of Diseases.

TABLE 13-2.

Unadjusted Analyses for Baseline and Interval History of Liver Disease by Group (Verified by Medical Record Review)

		Group					
		Ranch Hand		Comparison			
Disease	Statistic	Number	Percent	Number	Percent	Est. Relative Risk (95% C.I.)	p-Value
Hepatitis (Viral and Alcoholic)	n	1,016		1,293			
	Yes	37	3.6	43	3.3	1.10 (0.70,1.72)	0.731
	No	979	96.4	1,250	96.7		
Jaundice	n	1,016		1,293			
	Yes	20	2.0	28	2.2	0.91 (0.51,1.62)	0.771
	No	996	98.0	1,265	97.8		
Cirrhosis	n	1,016		1,293			
	Yes	3	0.5	2	0.2	1.91 (0.32,11.46)	0.660
	No	1,013	99.5	1,291	99.8		
Enlarged Liver	n	1,016		1,293			
	Yes	17	1.7	24	1.9	0.90 (0.48,1.68)	0.874
	No	999	98.3	1,269	98.1		
Miscel-laneous Liver Disorders	n	1,016		1,293			
	Yes	17	1.7	13	1.0	1.68 (0.81,3.47)	0.195
	No	999	98.3	1,280	99.0		

TABLE 13-3.

Medical Record Verification of Reported Liver Symptoms and Diseases by Group (Baseline and Interval Questionnaires Combined)

Variable	Verification Status	Group		p-Value
		Ranch Hand	Comparison	
Hepatitis	Number Reported	47	53	
	Medical Records Reviewed	44	48	
	Medical Records Pending or Not Released	3	5	
	Number Verified	37	43	
	Percent Verified	78.7	81.1	0.806
Jaundice	Number Reported	43	59	
	Medical Records Reviewed	23	35	
	Medical Records Pending or Not Released	20	24	
	Number Verified	20	28	
	Percent Verified	46.5	47.5	0.999
Cirrhosis	Number Reported	7	3	
	Medical Records Reviewed	5	3	
	Medical Records Pending or Not Released	2	0	
	Number Verified	3	2	
	Percent Verified	42.9	66.7	0.999
Enlarged Liver	Number Reported	30	29	
	Medical Records Reviewed	29	29	
	Medical Records Pending or Not Released	1	0	
	Number Verified	17	24	
	Percent Verified	56.7	82.8	0.047
Miscellaneous Liver Disorders	Number Reported	21	14	
	Medical Records Reviewed	20	14	
	Medical Records Pending or Not Released	1	0	
	Number Verified	17	13	
	Percent Verified	94.4	92.9	0.627

Peptic Ulcer Diseases

The primary purpose of these analyses was to compare the ulcer disease experience of the Ranch Hand and Comparison groups. Since blood type has been reported to affect the incidence of peptic ulcer disease, blood type was used as a covariate in these analyses. The military medical and personnel records of the 2,309 study participants were reviewed to determine the blood type as recorded in these sources. The distribution of blood types in the two groups is shown in Table 13-4.

TABLE 13-4.

Unadjusted Analysis of Blood Type by Group

	Blood Type								
	O		A		B		AB		
Group	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Total*
Ranch Hand	378	45.4	334	40.1	87	10.5	33	4.0	832
Comparison	504	46.4	425	39.1	125	11.5	33	3.0	1,087
				p=0.60					

*184 Ranch Hands and 206 Comparisons missing from blood type analysis.

The blood type distribution was not significantly different in the two groups (p=0.60), and was similar to the distribution of blood types in the general U.S. white male population (p=0.57).

Both physical examination diagnoses and questionnare responses to questions concerning ulcers were used as sources of data on the occurrence of ulcer disease. A total of 58 participants was diagnosed as having ulcer disease at the time of the examination; however, 13 had to be deleted from the analyses of physical examination data and 15 from the analyses of questionnaires due to missing data on blood type. On questionnaires, 42 reported currently having ulcers and an additional 126 reported having had ulcers in the past. These data are summarized in Table 13-5.

A three-factor log-linear analysis (group, ulcer, blood type) of data from the physical examination showed a significant three-factor interaction, with the Ranch Hand rate being higher in blood types AB and O, and lower for types A and B (p=0.03). Stratified analyses of each blood type were conducted and did not reveal any statistically significant group differences. These data are shown in Table 13-6.

TABLE 13-5.

Frequency of Diagnosed and Reported Ulcer Disease by Group

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Total
Diagnosed Disease (Physical Examination Data)	n	832		1,087		1,919
	Yes	19	2.3	26	2.4	45
	No	813	97.7	1,061	97.6	1,874
Reported Disease (Questionnaire Data)	n	832		1,085		1,917
	Current	22	2.6	20	1.8	44
	Past	53	6.4	73	6.7	126
	None	757	91.0	992	91.4	1,749

A three-factor log-linear analysis of questionnaire data was also performed. This analysis looked at current and past history of ulcer disease. No significant group differences or multifactor interactions were seen, with all p-values being greater than 0.10.

These analyses demonstrated overall group equivalence within the Ranch Hand and Comparison groups with respect to blood type and present and past ulcer disease.

Mortality Count Data

Linkage of digestive system mortality to observed historic or examination morbidity has not been explored in this report; the linkage process, with the use of the Comparison replacement strategy, remains an open research issue. From a broader perspective, however, review of mortality count data in conjunction with current morbidity data may be useful in identifying disease pattern(s) with respect to group membership, organ-specific disease, and important covariates. For these purposes, the latest mortality count data (as of 31 December 1985) are summarized in Table 13-7.

These data showed a large mortality contribution (approximately 50%)from liver disease in both groups and a relative excess in Ranch Hands as contrasted to Comparisons. For malignant neoplasms, there was a relative excess in the Comparison group. There is also the suggestion that alcohol is an important risk factor. The relative excess of malignant neoplasms in the Comparison group is also striking. Overall, the slight excess of digestive system mortality in the Ranch Hands and the differences in distribution of

TABLE 13-6.

Unadjusted Analyses of Peptic Ulcer Disease by Blood Type by Group

		Group					
		Ranch Hand		Comparison			
Blood Type	Statistic	Number	Percent	Number	Percent	Est. Relative Risk (95% C.I.)	p-Value
0	n	378		504			
	Yes	13	3.4	11	2.2	1.60 (0.70,3.60)	0.37
	No	365	96.6	493	97.8		
A	n	334		425			
	Yes	4	1.2	12	2.8	0.42 (0.14,1.29)	0.21
	No	330	98.8	413	97.2		
B	n	87		125			
	Yes	0	0.0	3	2.4	--	0.27[a]
	No	87	100.0	122	97.6		
AB	n	33		33			
	Yes	2	6.1	0	0.0	--	0.49[a]
	No	31	93.9	33	100.0		

--Estimated relative risk and confidence interval not calculated due to zero count in a cell.

[a]Fisher's exact test.

TABLE 13-7.

Frequency of Digestive System Mortality by Group

ICD Code	Deaths, by Group	
	Ranch Hand	1:5 Comparison
Pancreatitis (5770)	1	2
Alcoholic cirrhosis (5712)	0	6
Nonalcoholic cirrhosis (5715)	3	5
Nonalcoholic fatty liver (5718)	0	1
Chronic liver disease (5728)	1	1
Alcoholic liver disease (5711)	1	0
Duodenal ulcer (5325)	0	1
Malignant neoplasm (150-159)	2	15
Total	8	31

deaths by cause in the two groups raise the issue of competing mortality. Interpretation of the analyses in this report of hepatic function and liver disease, with alcohol consumption taken into account, should be reviewed in the light of these mortality data.

Physical Examination Data

Gastrointestinal dysfunction was not a major focus of the physical examination except for a comprehensive biochemical profile of the liver. Consequently, only data on hepatomegaly were analyzed, and results of the analysis are shown in Table 13-8.

The analysis showed a marginally significant excess (eight cases versus three) of hepatomegaly in the Ranch Hands ($p=0.069$). These results were in relative contrast to the Baseline examination findings of 1.56 percent and 0.78 percent in the Ranch Hand and Comparison groups, respectively ($p=0.138$), in the sense that fewer abnormalities were detected at the followup, although at both examinations the difference favored the Comparisons.

The group data for hepatomegaly were pooled and compared to the covariates of age, race, occupation, current alcohol use (one or less drinks per day, more than one to four drinks per day, and more than four drinks per day), lifetime exposure to industrial chemicals, and lifetime exposure to degreasing chemicals. Only age and occupation showed significant associations with hepatomegaly ($p=0.018$, $p=0.026$, respectively). Because of sparse data, an adjusted analysis was not conducted.

General Laboratory Examination Data

As in the Baseline Report, the followup examination emphasized evaluation of laboratory data, particularly for hepatic function. Thus, this

TABLE 13-8.

Unadjusted Analysis of Enlarged Livers Diagnosed at Physical Examination by Group*

	Enlarged Liver					
	Yes		No			
Group	Number	Percent	Number	Percent	Total	p-Value
Ranch Hand	8	0.8	1,002	99.2	1,010	0.069
Comparison	3	0.2	1,287	99.8	1,290	

*Excludes participants with positive HB_sAg.

section reports on nine laboratory tests of hepatic function and on two tests reflecting porphyrin metabolism. Normal ranges for these 11 variables as determined by the SCRF and the Mayo Clinic Laboratories are presented in Table 13-9. Only values greater than the normal range were considered important in the assessment of dysfunction.

Analyses of the nine hepatic variables were adjusted for the covariates of age, race, occupation (OCC), current alcohol use (ALC), days of exposure to industrial chemicals (IC), and days of exposure to degreasing chemicals (DC). For the two porphyrin analyses, blood urea nitrogen was used as a covariate. Because the hepatic test variables encompass acute to chronic effects, there was no "ideal" alcohol covariate (e.g., drink-years, current alcohol consumption in drinks per day).

The covariate alcohol use was obtained from questionnaire data, centering on daily alcohol consumption (beer, wine, liquor) for those participants who reported drinking at least one drink in the 2 weeks preceding the examination. Thus, the alcohol covariate measures recent drinking intensity and may be more useful in adjustment of acute variables (e.g., GGTP, SGPT) than variables related to chronic liver dysfunction (e.g., bilirubin determinations, alkaline phosphatase).

Exposure to industrial chemicals and degreasing chemicals was measured in cumulative days of unprotected exposure, and was derived from the 1982 and 1985 questionnaires. These data, therefore, represent lifetime exposure.

Exclusion categories consisted of fever (over 100 degrees Fahrenheit) and positive HB_sAg tests, because of the known effects of these conditions on liver function tests. Three participants (two Ranch Hands, one Comparison) were excluded because of fever, and eight (five Ranch Hands, three Comparisons) because of a positive HB_sAg test (seven positive, one missing). In addition, due to missing alcohol data, nine other individuals (six Ranch Hands, three Comparisons) were deleted from the analyses when current alcohol use was found to be a significant covariate.

TABLE 13-9.

Laboratory Norms for Nine Hepatic Function Variables and Two Porphyrin Determinations

Variable	Unit	SCRF Normal	SCRF Abnormal
SGOT	U/L	27-47	≥48
SGPT	U/L	3-36	≥37
GGTP	U/L	15-85	≥86
Alkaline Phosphatase	U/L	50-136	≥137
Total Bilirubin	mg/dl	≤1.5	>1.5
Direct Bilirubin	mg/dl	≤0.36	≥0.37
LDH	U/L	100-190	≥191
Cholesterol[a]	mg/dl	≤260	≥261
Triglycerides[a]	mg/dl	≤320	≥321
Uroporphyrin[b]	mg/24 hrs	≤46	≥47
Coproporphyrin[b]	mg/24 hrs	≤96	≥97

[a]SCRF provides age-dependent normal ranges; these values represent the maximum normal limits for those older than 40.

[b]Performed at the Mayo Clinic.

Statistical Analyses

The nine dependent variables from the hepatic battery were subjected to three types of basic analyses: (1) a continuous dependent variable adjusted by continuous covariates (CC), (2) a continuous dependent variable adjusted by discrete covariates (CD), and (3) a discrete (categorical) dependent variable adjusted by discrete covariates (DD), except for current alcohol use, which was left as a continuous variable for model-fitting and power purposes. General linear models (SAS®) were used for the CC and CD analyses, and BMDP®-LR was used for the DD analyses.

As noted in Chapter 7, Statistical Methods, all adjustments were carried out with the simplest model, including all significant covariates and two- and three-way interactions. The log transformation was used for the nine hepatic variables and for uroporphyrin, while a square root transformation was employed for the coproporphyrin variable. Since some direct bilirubin values were 0, the value 0.10 was added prior to log transformation.

The sample sizes were sufficient to detect a 1.93-fold increase in the frequency of abnormal values for alkaline phosphatase and a 1.42-fold increase in the frequency of abnormal values for SGPT, using a (two-sided) α-level of 0.05 and power 0.80. Further, the sample sizes were sufficient to detect a 0.7 percent mean shift in alkaline phosphatase, a 1.8 percent mean shift in SGPT, and a 2.8 percent mean shift in uroporphyrin values.

The results of the analyses on the 11 dependent variables are presented in the following summary tables (Tables 13-10 through 13-12), followed by descriptive narrative text. The summary tables are in the following logical order: unadjusted results, covariate tests of association, and adjusted results. Tables K-1 and K-2 of Appendix K summarize interactions from the statistical analyses. All analytic information on any given variable can be obtained by scanning the summary tables.

The following discussion condenses the key information on each dependent variable. Group-by-covariate interactions are narratively presented. The variables are organized in the same order as given in the tables.

Serum Glutamic-Oxaloacetic Transaminase (SGOT)

The unadjusted continuous (group means) and categorical (percent abnormalities) tests showed no statistically significant differences between groups ($p=0.298$ and $p=0.999$, respectively).

Tests of association with the covariates using pooled group categorical data demonstrated the significant effect of race (a higher percentage of abnormalities in Blacks than nonblacks, 13.5% versus 7.6%; $p<0.022$) and current alcohol use (21.2% abnormal values associated with more than four drinks per day, 9.0% abnormals for more than one to four drinks per day, and 5.8% for one or less drinks per day; $p<0.001$). Similarly, the mean SGOT levels differed significantly between races ($p<0.001$) and by current alcohol use ($p<0.001$).

The CC adjusted model showed no significant group differences ($p=0.309$). Significant covariates were race, an interaction of current alcohol use-by-degreasing chemicals, and an interaction of current alcohol use-by-age (all

TABLE 13-10.

Unadjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
SGOT	n	1,009	1,289		
	Mean	33.5	33.0		0.298
	95% C.I.	(32.8,34.1)	(32.5,33.5)		
	Number/%				
	Normal	929 92.1%	1,187 92.1%	1.00 (0.74,1.36)	0.999
	High	80 7.9%	102 7.9%		
SGPT	n	1,009	1,289		
	Mean	21.6	22.5		0.051
	95% C.I.	(20.9,22.3)	(21.9,23.1)		
	Number/%				
	Normal	872 86.4%	1,102 85.5%	0.93 (0.73,1.17)	0.546
	High	137 13.6%	187 14.5%		
GGTP	n	1,009	1,289		
	Mean	32.8	32.4		0.632
	95% C.I.	(31.4,34.3)	(31.2,33.6)		
	Number/%				
	Normal	919 91.1%	1,172 90.9%	0.98 (0.74,1.31)	0.942
	High	90 8.9%	117 9.1%		
Alkaline Phospha-tase	n	1,009	1,289		
	Mean	91.8	89.3		0.009
	95% C.I.	(90.4,93.3)	(88.1,90.6)		
	Number/%				
	Normal	953 94.5%	1,236 95.9%	1.37 (0.93,2.01)	0.114
	High	56 5.6%	53 4.1%		
Total Bilirubin	n	1,009	1,289		
	Mean	0.74	0.75		0.576
	95% C.I.	(0.73,0.76)	(0.74,0.76)		
	Number/%				
	Normal	982 97.3%	1,250 97.0%	0.88 (0.54,1.45)	0.706
	High	27 2.7%	39 3.0%		

TABLE 13-10. (continued)

Unadjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
Direct Bilirubin	n	1,009	1,289		
	Mean	0.18	0.18		0.981
	95% C.I.	(0.17,0.18)	(0.17,0.18)		
	Number/%				
	Normal	971 96.2%	1,246 96.7%	1.13 (0.73,1.77)	0.649
	High	38 3.8%	43 3.3%		
LDH	n	1,009	1,289		
	Mean	123.5	123.9		0.655
	95% C.I.	(122.2,124.8)	(122.7,125.2)		
	Number/%				
	Normal	999 99.0%	1,272 98.7%	0.75 (0.34,1.64)	0.560
	High	10 1.0%	17 1.3%		
Cholesterol	n	1,009	1,289		
	Mean	214.3	215.0		0.688
	95% C.I.	(211.8,216.8)	(212.8,217.2)		
	Number/%				
	Normal	863 85.5%	1,082 83.9%	0.88 (0.70,1.11)	0.322
	High	146 14.5%	207 16.1%		
Triglycerides	n	1,009	1,289		
	Mean	118.5	117.3		0.719
	95% C.I.	(113.8,123.3)	(113.4,121.4)		
	Number/%				
	Normal	941 93.3%	1,210 93.9%	1.11 (0.79,1.55)	0.549
	High	68 6.7%	79 6.1%		
Uroporphyrin	n	1,006	1,286		
	Mean	16.9	17.9		0.048
	95% C.I.	(16.2,17.7)	(17.3,18.6)		
Copropor-phyrin	n	1,008	1,287		
	Mean	119.1	115.6		0.081
	95% C.I.	(116.2,122.0)	(113.0,118.2)		

TABLE 13-11.

Association Between Nine Hepatic Function Variables and Two Porphyrin Determinations and Six Covariates in the Combined Ranch Hand and Comparison Groups

Variable	Analysis*	Age	Race	Occupation	Alcohol	Industrial Chemicals	Degreasing Chemicals
SGOT	C	NS	<0.001	NS	<0.001	NS	NS
	D	NS	0.022	NS	<0.001	NS	NS
SGPT	C	<0.001	NS	NS	<0.001	NS	0.017
	D	0.001	NS	NS	<0.001	NS	NS
GGTP	C	0.012	<0.001	0.032	<0.001	NS	NS
	D	NS	0.021	NS	<0.001	NS	NS
Alkaline Phosphatase	C	NS	NS	<0.001	<0.001[a]	<0.001	0.010
	D	NS	NS	0.003	NS*[a]	0.030	NS*
Total Bilirubin	C	NS*	NS	0.011	0.008	NS	NS
	D	NS	<0.001	NS	NS	NS	NS
Direct Bilirubin	C	NS	NS*	NS	<0.001	NS	NS
	D	NS	0.015	NS	NS	NS	NS
LDH	C	<0.001	0.006	NS	NS	NS	NS
	D	NS	NS	NS	NS	NS	NS
Cholesterol	C	<0.001	NS	0.002	<0.001	NS	NS
	D	0.010	NS	0.008	0.018	NS	NS
Triglycerides	C	<0.001	<0.001	0.013	0.030	NS*	0.019
	D	NS	0.031	NS	NS	NS*	NS
Uroporphyrins	C	NS	NS	NS	NS	NS	NS
Coproporphyrins	C	0.003	NS	NS	<0.001	NS	NS

*Continuous (C)/Discrete (D).

NS: Not significant ($p>0.10$)

NS*: Borderline significant ($0.05<p\leq 0.10$).

[a]Wine consumption.

TABLE 13-12.

Adjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Analysis	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
SGOT	CC	n	1,003	1,286			ALC*DC(p<0.001)
		Adj. Mean	34.8	34.3	—	0.309	AGE*ALC(p<0.001)
		95% C.I.	(33.8,35.7)	(33.4,35.3)			RACE(p<0.001)
	CD	n	1,003	1,286			GRP*ALC(p=0.048)
		Adj. Mean	****	****	—	****	ALC*IC(p=0.008)
		95% C.I.	****	****			DC(p=0.019), RACE(p<0.001)
	DD	n	1,003	1,286	1.03 (0.75,1.41)	0.868	AGE*ALC(p<0.001)
							OCC*ALC(p<0.001)
							RACE (p=0.026)
SGPT	CC	n	1,003	1,286			ALC*DC(p=0.008), RACE*DC(p=0.015)
		Adj. Mean	21.4	22.2	—	0.048	AGE*ALC(p=0.001), RACE*IC(p=0.017)
		95% C.I.	(20.4,22.4)	(21.3, 23.3)			
	CD	n	1,003	1,286			ALC*DC(p=0.032), AGE*ALC(p=0.022)
		Adj. Mean	21.9	22.9	—	0.029	OCC*AGE(p=0.026), IC(p=0.049)
		95% C.I.	(20.2,23.8)	(21.1,24.8)			
	DD	n	1,003	1,286	0.93 (0.73,1.18)	0.531	AGE*ALC(p=0.004)
GGTP	CC	n	1,003	1,286			AGE*ALC(p<0.001),RACE*IC(p=0.011)
		Adj. Mean	37.5	37.0	—	0.575	ALC*DC(p<0.001), AGE*DC(p=0.009)
		95% C.I.	(35.2,40.1)	(34.7,39.3)			
	CD	n	1,003	1,286			AGE*ALC(p=0.023), OCC*ALC(p=0.044)
		Adj. Mean	44.1	43.6	—	0.668	RACE(p<0.001)
		95% C.I.	(40.0,48.6)	(39.6,47.9)			
	DD	n	1,003	1,286	1.00 (0.74,1.34)	0.971	AGE*ALC(p<0.001), RACE(p=0.016)

TABLE 13-12. (continued)

Adjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Analysis	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Alkaline Phosphatase	CC	n	1,003	1,285	—	0.008	AGE*IC(p=0.010), RACE*IC(p=0.007) OCC(p<0.001), WINE(p<0.001)
		Adj. Mean	91.6	89.1			
		95% C.I.	(89.4,93.9)	(87.0,91.2)			
	CD	n	1,003	1,285	—	****	GRP*IC(p=0.011), AGE*IC(p=0.019) RACE*IC(p=0.002), OCC(p<0.001) WINE (p<0.001)
		Adj. Mean	****	****			
		95% C.I.	****	****			
	DD	n	1,003	1,285	1.44 (0.97,2.13)	0.070	WINE*DC(p=0.006), AGE*IC(p=0.005) RACE*IC(p=0.004), OCC*IC(p=0.016)
Total Bilirubin	CC	n	1,003	1,286	—	0.599	AGE*DC(p=0.039) RACE*ALC(p=0.007) RACE*OCC(p=0.001)
		Adj. Mean	0.78	0.78			
		95% C.I.	(0.75,0.81)	(0.75,0.81)			
	CD	n	1,003	1,286	—	0.598	RACE*ALC(p=0.004) OCC*ALC(p=0.034) OCC*RACE(p=0.002)
		Adj. Mean	0.83	0.83			
		95% C.I.	(0.79,0.87)	(0.80,0.87)			
	DD	n	1,009	1,289	0.89 (0.54,1.47)	0.648	RACE(p<0.001)
Direct Bilirubin	CC	n	1,003	1,286	—	0.972	RACE*ALC(p=0.025)
		Adj. Mean	0.18	0.18			
		95% C.I.	(0.17,0.20)	(0.17,0.19)			
	CD	n	1,003	1,286	—	0.830	DC*IC(p=0.025), ALC*DC(p=0.012) RACE*ALC(p=0.019), OCC*ALC(p=0.002)
		Adj. Mean	0.21	0.20			
		95% C.I.	(0.19,0.22)	(0.19,0.22)			
	DD	n	1,003	1,286	****	****	GRP*IC(p=0.012), RACE(p=0.014) ALC(p=0.026)

TABLE 13-12. (continued)

Adjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Analysis	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Realtive Risk (95% C.I.)	p-Value	Covariate Remarks*
	CC	n	1,003	1,286			GRP*AGE(p=0.018), OCC*IC(p=0.014)
		Adj. Mean	****	****	—	****	RACE*IC(p=0.024)
		95% C.I.	****	****			
LDH	CD	n	1,003	1,286			RACE(p<0.001), AGE(p<0.001)
		Adj. Mean	130.0	130.5	—	0.671	DC(p=0.016)
		95% C.I.	(127.3,132.8)	(127.8,133.1)			
	DD	n	1,009	1,289	0.75 (0.34,1.64)	0.560	
	CC	n	1,003	1,286			RACE*DC(p=0.021), RACE*OCC(p=0.005)
		Adj. Mean	219.5	220.4	—	0.604	IC(p=0.043), ALC(p<0.001)
		95% C.I.	(214.5,224.7)	(215.5,225.4)			AGE(p<0.001)
Cholesterol	CD	n	1,003	1,286			RACE*OCC(p=0.027), ALC(p<0.001)
		Adj. Mean	223.8	224.9	—	0.548	AGE(p<0.001)
		95% C.I.	(217.7,230.1)	(218.9,231.0)			
	DD	n	1,003	1,286	0.85 (0.68,1.08)	0.181	RACE*ALC(p=0.012), AGE(p=0.029)
							OCC(p=0.039)
	CC	n	1,003	1,286			GRP*AGE(p=0.015), ALC*DC(p=0.005)
		Adj. Mean	****	****	—	****	RACE*ALC(p=0.031), OCC(p<0.001)
		95% C.I.	****	****			
Triglycerides	CD	n	1,003	1,286			OCC(p<0.001), RACE(p<0.001)
		Adj. Mean	112.5	112.1	—	0.905	AGE(p<0.001), ALC(p=0.038)
		95% C.I.	(103.7,121.9)	(103.7,121.2)			
	DD	n	1,009	1,289	****	****	GRP*OCC(p=0.027), RACE (p=0.026)
							IC(p=0.038)

TABLE 13-12. (continued)

Adjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Analysis	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Uroporphyrin	CC	n	1,000	1,283			GRP*BUN(p=0.015)
		Adj. Mean	****	****	—	****	DC*OCC(p=0.005)
		95% C.I.	****	****			ALC(p=0.026)
Coproporphyrin	CC	n	1,002	1,284			AGE*ALC(p=0.003)
		Adj. Mean	119.3	115.7	—	0.065	BUN(p<0.001)
		95% C.I.	(116.4,122.2)	(113.2,118.2)			

*Abbreviations:
GRP: group
OCC: occupation
ALC: current alcohol use
WINE: wine consumption
DC: exposure to degreasing chemicals
IC: exposure to industrial chemicals
BUN: blood urea nitrogen

— No relative risk or confidence interval given for continuous analyses.
**** Group-by-covariate interaction—adjusted mean/relative risk, confidence interval, and p-value are not presented.

with p<0.001). The CD analysis revealed a significant group (GRP)-by-current alcohol use interaction (p=0.048), precluding a direct group contrast. Exploration of the interaction disclosed that the Ranch Hands had a significantly higher (p=0.010) mean SGOT for the more than one to four drinks per day category, whereas there were no significant group differences for the one or less drinks per day or more than four drinks per day categories (see Table K-1 of Appendix K). Other significant covariate effects included degreasing chemicals (p=0.019), race (p<0.001), and a current alcohol use-by-industrial chemical (IC) interaction (p=0.008). The DD SGOT analysis showed no significant group differences (p=0.868). Covariates making significant contributions were race (p=0.026), an age-by-current alcohol use interaction (p<0.001), and an occupation (OCC)-by-current alcohol use interaction (p<0.001).

Serum Glutamic-Pyruvic Transaminase (SGPT)

The unadjusted categorical analysis was not significant (p=0.546), but the comparison of group means showed a borderline significant result, with the Comparisons having a higher mean SGPT than the Ranch Hands (p=0.051).

Covariate associations with the pooled categorical Ranch Hand and Comparison group data showed an inverse relationship (p=0.001) between SGPT levels and age, with 17.1 percent abnormalities for those born in or after 1942, 12.3 percent for those born between 1923 and 1941, and 8.1 percent for those born in or before 1922. The relationship with current alcohol use was also profound (p<0.001), with 23.4 percent abnormals noted for more than four drinks per day, 15.3 percent abnormals for more than one to four drinks per day, and 12.4 percent for one or less drinks per day. The direction and magnitude of the covariate effects of age and alcohol were quite similar for the tests of association with the mean SGPT level of both groups (p<0.001 for both covariates).

No significant group interactions were detected in either the discrete or the continuous analyses. The CC-adjusted analysis yielded a significant group difference, with the Comparisons having a higher group mean than the Ranch Hands (p=0.048). The model was adjusted by the interactions of current alcohol use-by-degreasing chemicals (p=0.008), current alcohol use-by-age (p=0.001), race-by-degreasing chemicals (p=0.015), and race-by-industrial chemicals (p=0.017). The CD model also showed a significantly elevated mean SGPT in the Comparison group (p=0.029). The analysis was adjusted for exposure to industrial chemicals (p=0.049), and the interactions of age-by-occupation (p=0.026), age-by-current alcohol use (p=0.022), and current alcohol use-by-degreasing chemicals (p=0.032). A borderline significant interaction (p=0.0505) between group and current alcohol use was found, but because of modeling strategy, this interaction was not included in the final model. (This interaction is explored further in Table K-1 in Appendix K, however.) The DD-adjusted analysis, like the unadjusted discrete analysis, disclosed a nonsignificant group difference (p=0.531). The model was adjusted for an age-by-current alcohol use interaction (p=0.004).

Gamma-Glutamyl Transpeptidase (GGTP)

The unadjusted contrasts of both mean levels of GGTP and the frequency of abnormalities showed no significant differences between the Ranch Hand and Comparison groups (p=0.632 and p=0.942, respectively).

For discrete covariate associations, significance was noted for race, with 14.9 percent abnormals in Blacks and 8.6 percent for nonblacks ($p=0.021$), and current alcohol use, with 26.1 percent abnormals for more than four drinks per day, 10.5 percent for more than one to four drinks per day, and 6.2 percent for one or less drinks per day use ($p<0.001$). While the mean level of GGTP was similarly affected by race and current alcohol ($p<0.001$ for both covariates), it was also influenced by age (30.3 U/L for those born in or before 1922, 33.9 U/L for those born between 1923 and 1941, and 31.1 U/L for those born in or after 1942; $p=0.012$) and occupation (31.5 U/L for officers, 35.2 U/L for enlisted flyers, and 32.5 U/L for enlisted groundcrew; $p=0.032$).

Each of the three adjusted analyses consistently produced nonsignificant group differences (CC: $p=0.575$; CD: $p=0.668$; DD: $p=0.971$). None of the three models was affected by a group-by-covariate interaction. The CC analysis was adjusted by four covariate interactions: age-by-current alcohol use ($p<0.001$), race-by-industrial chemicals ($p=0.011$), current alcohol use-by-degreasing chemicals ($p<0.001$), and age-by-degreasing chemicals ($p=0.009$). The CD model was adjusted by race ($p<0.001$), by an age-by-current alcohol use interaction ($p=0.023$), and by an occupation-by-current alcohol use interaction ($p=0.044$). The DD analysis was adjusted by race ($p=0.016$) and by an age-by-current alcohol use interaction ($p<0.001$).

Alkaline Phosphatase

The analysis of group mean values showed a significantly higher ($p=0.009$) Ranch Hand mean (91.8 U/L) than that observed in the Comparison group (89.3 U/L). The unadjusted categorical analysis revealed a higher percentage of Ranch Hand abnormalities (5.6%) than Comparison abnormalities (4.1%), but this difference was not significant (Est. RR=1.37, 95% C.I.: [0.93,2.01], $p=0.114$).

With pooled group data, significant covariate associations were found between the proportion of abnormal values and occupation ($p=0.003$), industrial chemicals ($p=0.030$), and marginally significant associations with wine consumption ($p=0.056$) and degreasing chemicals ($p=0.091$). The mean value of alkaline phosphatase depended significantly on all four of these covariates.

The CC-adjusted analysis also showed a significantly higher mean value of alkaline phosphatase in the Ranch Hand group ($p=0.008$). The model was adjusted by the significant covariates of wine consumption (WINE) ($p<0.001$), occupation ($p<0.001$), and the interactions of age-by-industrial chemicals ($p=0.010$) and race-by-industrial chemicals ($p=0.007$). Wine consumption was used as a covariate instead of alcohol intensity since wine showed a very strong negative association with alkaline phosphatase. This effect masked a very weak positive association between beer or liquor consumption and alkaline phosphatase.

In the CD model a significant group-by-industrial chemicals interaction was found ($p=0.011$). Specifically, in those individuals exposed to industrial chemicals, the Ranch Hands had a significantly higher mean value than the Comparisons ($p<0.001$), whereas in the unexposed stratum, the mean values were not significantly different between groups ($p=0.973$; see Table K-1 of Appendix K). The CD analysis was also adjusted by wine consumption ($p<0.001$), occupation ($p<0.001$), and the interactions of age-by-industrial chemicals ($p=0.019$) and race-by-industrial chemicals ($p=0.002$).

The DD model revealed a marginally significant group difference (Adj. RR: 1.44, 95% C.I.: [0.97,2.13], p=0.070) following adjustment by four significant interactions of wine-by-degreasing chemicals (p=0.006), age-by-industrial chemicals (p=0.005), race-by-industrial chemicals (p=0.004), and occupation-by-industrial chemicals (p=0.016).

Total Bilirubin

Both the continuous and categorical unadjusted analyses found no significant differences in total bilirubin values between groups (p=0.576 and p=0.706, respectively).

The covariate associations for both groups showed a significant effect of race (8.5% abnormal in Blacks versus 2.5% in nonblacks; p<0.001). Significant differences in mean total bilirubin levels were found between occupational groups (0.76 mg/dl for officers, 0.72 mg/dl for enlisted flyers, and 0.75 mg/dl for enlisted groundcrew; p=0.011), and with increasing levels of current alcohol use (0.80 for more than four drinks per day, 0.75 for more than one to four drinks per day, and 0.74 for one or less drinks per day; p=0.008). Further, increasing levels of total bilirubin were marginally associated with age (p=0.093).

The CC model, adjusted for the interactions of age-by-degreasing chemicals (p=0.039), race-by-current alcohol use (p=0.007), and race-by-occupation (p=0.001), revealed no significant differences in total bilirubin means between groups (p=0.599). Similarly, the CD analysis found no difference between group means (p=0.598) after adjustment for the interactions of race-by-current alcohol use (p=0.004), occupation-by-current alcohol use (p=0.034), and occupation by race (p=0.002). The DD model, adjusted for race (p<0.001), also failed to detect significant group differences in the proportion of total bilirubin abnormalities (p=0.648).

Direct Bilirubin

Neither the continuous nor the categorical unadjusted tests disclosed significant differences between the Ranch Hand and Comparison groups (p=0.981 and p=0.649, respectively).

A covariate association with the categorical data combined from both groups was noted for race, with 7.8 percent abnormalities found in Blacks as contrasted to 3.3 percent in nonblacks (p=0.015). There was a significant association between mean values of direct bilirubin and current alcohol use (0.21 mg/dl, 0.17 mg/dl, and 0.17 mg/dl for more than four drinks per day, more than one to four drinks per day, and one or less drinks per day, respectively; p<0.001) and a marginally significant difference due to race (0.20 mg/dl for Blacks versus 0.18 mg/dl for nonblacks; p=0.059).

For both the CC and CD analyses, no significant group differences were found (p=0.972 and p=0.830, respectively). The CC model was adjusted for a race-by-current alcohol use interaction (p=0.025), and the CD model was adjusted for the significant interactions of race-by-current alcohol use (p=0.019), occupation-by-current alcohol use (p=0.002), current alcohol use-by-degreasing chemicals (p=0.012), and degreasing chemicals-by-industrial chemicals (p=0.025). The DD analysis revealed a group-by-industrial chemical

exposure interaction (p=0.012). For participants exposed to industrial chemicals, the Ranch Hands had a higher proportion with abnormal values than the Comparisons (5.3% abnormal versus 2.9%, respectively; p=0.035), whereas there was no group difference for participants not exposed to industrial chemicals (p=0.144). Each stratum of the interaction was adjusted for race (p=0.014) and current alcohol use (p=0.026). The biological relevance of this interaction is unclear at this time.

Lactic Dehydrogenase (LDH)

No significant differences were found between the groups, either in the proportion of abnormal values (p=0.560) or in the mean levels of LDH (p=0.655). Significant effects for age (121.6 U/L, 124.6 U/L, 135.3 U/L for those born in or after 1942, between 1923 and 1941, and in or before 1922, respectively; p<0.001) and race (129.5 U/L for Blacks versus 123.4 U/L for nonblacks; p=0.006) were found in the tests of mean LDH levels.

The CC analysis revealed a group-by-age interaction (p=0.018), although no significant adjusted group differences were found for any of the three age strata. The model was also adjusted for the significant interactions of occupation-by-exposure to industrial chemicals (p=0.014) and race by exposure to industrial chemicals (p=0.024). The CD model revealed no significant group differences after adjustment by age (p<0.001), race (p<0.001), and degreasing chemicals (p=0.016). Similarly, the DD analysis found no significant group differences, and no covariates made a significant contribution to the model.

Cholesterol

No significant differences were found between groups, either in the proportion of abnormal cholesterol levels (p=0.322) or in mean values of cholesterol (p=0.688) by unadjusted tests. However, in contrast, analysis of the Ranch Hand group versus the Original Comparisons (see Table K-9 of Appendix K) showed that the Comparisons had a significantly higher proportion of abnormal levels than the Ranch Hands (18.3% versus 14.5%, respectively; Est. RR: 0.76, 95% C.I.: [0.60,0.96], p=0.023). This observation was also found at Baseline. Significant covariate associations were noted between the proportion of participants with abnormally high cholesterol levels and age (12.7% for those born in or after 1942, 17.2% for those born between 1923 and 1941, and 18.4% for those born in or before 1922; p=0.010), occupation (14.9% for officers, 20.5% for enlisted flyers, and 13.9% for enlisted groundcrew; p=0.008), and current alcohol use (14.1% for one or less drinks per day, 16.4% for more than one to four drinks per day, and 21.7% for more than four drinks per day; p=0.018). For the associations between mean cholesterol levels and age, occupation, and current alcohol use, the significance of the covariate effects was greater than for the discrete analyses (p<0.001, p=0.002, and p<0.001, respectively).

The CC results showed no significant group difference (p=0.604). The model was adjusted by age (p<0.001), current alcohol use (p<0.001), industrial chemical exposure (p=0.043), and the race-by-degreasing chemicals (p=0.021) and race-by-occupation (p=0.005) interactions. The CD analysis was negative for significant group differences (p=0.548). The analysis included the covariate contributions made by age (p<0.001), current alcohol use

($p<0.001$), and a race-by-occupation interaction ($p=0.027$). The DD analysis also showed no significant difference between groups for adjusted proportions of participants with abnormal cholesterol levels ($p=0.181$). Contributing covariates included age ($p=0.029$), occupation ($p=0.039$), and a race-by-current alcohol use interaction ($p=0.012$). In all of the discrete cholesterol analyses, the cutpoint of 260 mg/dl was used.

Triglycerides

In the unadjusted analyses, no significant differences in the proportion of participants with abnormal triglyceride levels or in mean values were found between the Ranch Hand and Comparison groups ($p=0.549$ and $p=0.719$, respectively).

The covariate tests of association for percent abnormal triglycerides disclosed the significant effect of race (2.1% for Blacks and 6.7% for nonblacks; $p=0.031$) and a marginally significant association for industrial chemical exposure ($p=0.073$). For mean triglyceride levels, significant associations for age ($p<0.001$), race ($p<0.001$), occupation ($p=0.013$), current alcohol use ($p=0.030$), and degreasing chemicals ($p=0.019$) were noted, in addition to a marginally significant association with exposure to industrial chemicals ($p=0.077$).

The CC analysis revealed a significant group-by-age interaction ($p=0.015$), which showed a significantly elevated mean triglyceride level in Ranch Hands ($p=0.039$) born in or before 1922 as compared to similarly aged Comparisons (see Table K-1 of Appendix K). There were no significant differences for the other two age strata. A significant adjusting covariate was occupation ($p<0.001$); in addition, the current alcohol use-by-degreasing chemicals ($p=0.005$) and race-by-current alcohol use ($p=0.031$) interactions were used for adjustment. The CD-adjusted analysis found no significant group differences ($p=0.905$). The model was adjusted by age ($p<0.001$), race ($p<0.001$), occupation ($p<0.001$), and current alcohol use ($p=0.038$).

The DD analysis found a significant group-by-occupation interaction ($p=0.027$). Stratification by occupation revealed a significant increase in the proportion of abnormal triglyceride levels for Ranch Hand officers (Adj. RR: 1.77, 95% C.I.: [1.04,3.01], $p=0.035$) but no significant group differences were discerned for the enlisted flyer or enlisted groundcrew strata. The models were adjusted by race ($p=0.026$) and industrial chemical exposure ($p=0.038$). A cutpoint of 320 mg/dl was used to distinguish abnormal from normal.

Uroporphyrin

The uroporphyrin variable was analyzed only in the continuous form. The unadjusted analysis revealed a significant difference between group means (Comparisons 17.9 mg/24 hrs, Ranch Hands 16.9 mg/24 hrs; $p=0.048$).

A CC model found a significant group-by-blood urea nitrogen (BUN) interaction ($p=0.015$; see Table K-1 of Appendix K). To interpret the interaction, BUN was dichotomized at the median value of 14 mg/dl. Stratifying by BUN levels revealed a significantly greater ($p<0.001$) uroporphyrin mean for Comparisons than for Ranch Hands for BUN levels of 14 or less mg/dl and a non-significant but greater Ranch Hand mean for participants with BUN levels of

more than 14 mg/dl. The stratified model was adjusted for current alcohol use (p=0.026) and the occupation-by-degreasing chemicals (p=0.005) interaction.

Coproporphyrin

As with the uroporphyrin variable, coproporphyrin was analyzed only as a continuous variable. The unadjusted analysis revealed a borderline significant difference in the mean coproporphyrin levels (119.1 mg/24 hrs for Ranch Hands and 115.6 mg/24 hrs for Comparisons; p=0.081).

The covariate tests of association detected the significant effects of age (p=0.003) and current alcohol use (p=<0.001).

A CC model, adjusted by BUN (p<0.001) and an age-by-current alcohol use interaction (p=0.003) revealed a borderline significant group difference (p=0.065) similar to the unadjusted analysis. The adjusted coproporphyrin means were 119.3 mg/24 hrs and 115.7 mg/24 hrs for the Ranch Hands and Comparisons, respectively.

Discussion

The results from the nine hepatic and two porphyrin analyses were not totally consistent with the Baseline findings. Several analytical reasons may possibly explain some of these differences, i.e., the adjusted analyses herein used the additional covariates of age, race, and occupation (the matching variables), and all two-way covariate interactions. However, as the Baseline data were not reanalyzed with the model process and total Comparison group used in this report, the contribution of analytic technique versus a true change in hepatic status is unknown.

The Baseline Report noted a significantly lower mean cholesterol level in the Ranch Hands (opposite of an expected dioxin effect) and slight tendencies for higher GGTP and LDH values in the Ranch Hands. In this chapter, the analyses have shown equivalent group cholesterol levels, an increased SGPT mean in the Comparisons, an increased mean alkaline phosphatase in the Ranch Hands, an increased uroporphyrin mean in the Comparisons, and a borderline increased coproporphyrin mean in the Ranch Hands. The individual hepatic assay results were not suggestive of a pattern of significant hepatic damage in the Ranch Hands that might be supportive of an herbicide effect. Further, there was no consistent group-by-covariate interaction that suggests a detriment to a specific subcategory of the Ranch Hands.

For those covariates used in both the Baseline study and this followup study, the direction and magnitude of their effects were relatively consistent between the studies. However, an unexpected association between wine drinking and alkaline phosphatase lacks a plausible explanation, particularly considering the inverse relationship, i.e., increasing alkaline phosphatase levels with decreasing wine consumption. These findings suggested the association between wine and alkaline phosphatase may be due to imprecision in data collection.

None of the categorical (normal/abnormal categories) analyses was statistically significant, whereas all of the significant results were

generated by the more powerful contrasts of continuously distributed hepatic data.

Both porphyrin analyses showed group associations and are in distinct contrast to the otherwise largely negative hepatic findings. The significantly elevated uroporphyrin mean value in the Comparisons was directly opposite to that expected if dioxin-induced PCT were prevalent in the Ranch Hands. The primary biochemical defect in PCT is the reduced activity of uroporphyrinogen decarboxylase, an enzyme that metabolizes uroporphyrin. This defect leads to increased levels of uroporphyrin and coproporphyrin.

Questionnaire-Laboratory Correlations: Porphyria Cutanea Tarda

In the interval questionnaire all participants were asked whether their skin manifested "patches," excessive bruises, or sensitivity. These questions were deemed important in order to bound the maximum prevalence of cutaneous disorders compatible with a diagnosis of PCT. These historical data are given in Table 13-13.

TABLE 13-13.

Unadjusted Analysis for Interval History of Skin Bruises, Skin Patches, and Skin Sensitivity by Group

	Bruises, Patches, or Sensitivity					
	Yes		No			
Group	Number	Percent	Number	Percent	Total	p-Value
Ranch Hand	265	26.2	746	73.8	1,011	0.001
Comparison	260	20.2	1,029	79.8	1,289	

These data revealed that the Ranch Hands reported significantly more cutaneous symptoms (26.2%) than the Comparisons (20.2%). However, these data were substantially less than those reported at the Baseline in-home questionnaire, which also showed a statistically significant excess in the Ranch Hands.

To determine if the skin histories might be related to PCT, the historic data were compared to the porphyrin test results. The abnormal/normal cut-point of the coproporphyrin assays was reset to the 95th percentile because the normal range of the laboratory overclassified the proportion of abnormals. Table 13-14 gives the tabular display of both porphyrin test results by the reporting history of skin disorders.

TABLE 13-14.

Unadjusted Analyses for Porphyrin Abnormalities by Group and Skin Patch, Bruise, or Sensitivity Reported at Followup Questionnaire

Group	Skin Patch, Bruise, or Sensitivity Reported	Abnormal Porphyrin Findings for a Participant: 0 Number	0 Percent	1 Number	1 Percent	2 Number	2 Percent	Total	p-Value*
Both Groups	Yes	472	90.1	48	9.2	4	0.8	524	0.789
	No	1,593	90.2	165	9.3	9	0.5	1,767	
Ranch Hand	Yes	239	90.5	24	9.1	1	0.4	264	0.950
	No	670	90.3	70	9.4	2	0.3	742	
Comparison	Yes	233	89.6	24	9.2	3	1.2	260	0.742
	No	923	90.1	95	9.3	7	0.7	1,025	

*Chi-square test, 2 d.f.

The data from both groups combined suggest that there is no relationship between a history of cutaneous disorders and porphyrin test positivity. The group-specific data in the table also show a lack of a statistically significant association between the reporting of skin patches, bruises, or sensitivity and the presence of an abnormal porphyrin test result. However, in both the Ranch Hand and Comparison groups, participants who had abnormal tests for both uroporphyrins and coproporphyrins were more likely to have reported cutaneous disorders than participants with normal findings for both tests. Consequently, the data were retabulated, focusing only upon uroporphyrin abnormalities (absolutely required for a diagnosis of PCT) and reporting of cutaneous disorders. These data are summarized in Table 13-15.

These data suggest that the relative risk of increased uroporphyrin abnormalities for Ranch Hands is independent of whether or not a study participant reported skin patches, bruises, or sensitivities at the followup questionnaire (Breslow-Day test of homogeneity of odds ratio, p=0.791). In each instance (reported/not reported), the estimated relative risk was nonsignificant and less than 1, and in both the Ranch Hand group and the Comparison group there was a higher percentage of uroporphyrin abnormalities for participants who did not report skin patches, bruises, or sensitivity than for participants who did report these conditions.

Thus, the sequential displays of Tables 13-13 through 13-15 show excessive reporting of PCT-like cutaneous symptoms in the Ranch Hand group that was not related to test abnormalities for both uroporphyrin and coproporphyrin abnormal test results, or for uroporphyrin abnormalities alone. These analyses were consistent with the clinical observation that

TABLE 13-15.

Unadjusted Analyses for Uroporphyrin Abnormalities by Group and Skin Patch, Bruise, or Sensitivity Reported at Followup Questionnaire

Variable	Stratification	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Uroporphyrin								
Skin Patch, Bruise, or Sensitivity Reported		n	264		260			
		Abnormal	12	4.5	12	4.6	0.98 (0.43,2.23)	0.999
		Normal	252	95.5	248	95.4		
Skin Patch, Bruise, or Sensitivity Not Reported		n	742		1,025			
		Abnormal	42	5.7	66	6.4	0.89 (0.62,1.28)	0.547
		Normal	700	94.3	959	93.6		

only one differential diagnosis at the examination entertained the diagnosis of PCT. Based on all of these observations, PCT was a rare, if not non-existent, condition in the Ranch Hands.

EXPOSURE INDEX ANALYSES

Both unadjusted and adjusted exposure index analyses were carried out for the nine laboratory tests of hepatic function and the two porphyrin metabolite tests. The porphyrin variables were analyzed only as continuous variables, while the others were analyzed both as continuous variables and discretized variables. Five covariates were included in the adjusted analyses: age, race, current alcohol use, exposure to degreasing chemicals (yes/no), and exposure to industrial chemicals (yes/no). Current alcohol use was treated as a continuous variable for all adjusted analyses, and age was treated as a continuous variable for the continuous adjusted analyses. Age was trichotomized (born in or after 1942, born between 1923 and 1941, and born in or before 1922) for the discrete adjusted analyses. In addition, the covariate BUN was used in the porphyrin analyses.

For each variable, exposure level frequencies and percents are presented in Table K-3 of Appendix K along with the results of the unadjusted discrete

analyses using Pearson's chi-square test to reflect overall exposure index differences and Fisher's exact test to investigate medium versus low and high versus low exposure level contrasts. Unadjusted means for each exposure level are presented in Table K-4 of Appendix K, along with the results of the unadjusted continuous analyses (using an F-test for an overall group assessment) and t-tests to examine medium versus low and high versus low exposure index contrasts. Results of the adjusted categorical and adjusted continuous analyses are presented in Tables 13-16 and 13-17, respectively. These results are presented in the context of a main effects model containing exposure index and all five covariates. Additional adjusted continuous analyses were conducted to examine pairwise interactions involving the exposure index and the covariates. Unadjusted and adjusted results for each variable are discussed in sequence.

SGOT

Within each occupation cohort, the low exposure level had the lowest percentage of abnormalities and the lowest mean. A marginally significant overall exposure level relationship (p=0.065) was found in the unadjusted discrete analysis for the enlisted groundcrew. This association was statistically significant in the adjusted analysis (p=0.023), exhibiting a dose-response effect; medium versus low (Adj. RR: 2.14, 95% C.I.: [0.77,5.99], p=0.147) and high versus low (Adj. RR: 3.64, 95% C.I.: [1.36,9.72], p=0.010). A nonsignificant dose-response relationship was observed in the corresponding unadjusted and adjusted continuous analyses (p=0.418 and p=0.409, respectively), with unadjusted means of 32.9 U/L, 33.2 U/L, and 34.4 U/L for the low, medium, and high exposure levels, respectively. No significant results were found for enlisted flyers and officers.

SGPT

Within the enlisted groundcrew and enlisted flyer cohorts the low exposure level had the lowest percentage of abnormalities and the lowest mean value. This situation was reversed for the officers who exhibited the highest percentage of abnormal measurements and highest mean value in the low exposure categories. A significant overall result was found for enlisted flyers in the adjusted discrete analysis (p=0.036; medium versus low, Adj. RR: 6.55, 95% C.I.: [1.25,34.43], p=0.026); high versus low, Adj. RR: 4.29, 95% C.I.: [0.75,24.35], p=0.101). In the corresponding adjusted continuous analyses, a marginally significant dose-response relationship was observed (p=0.058) with adjusted means 18.1 U/L, 21.4 U/L, and 21.8 U/L for the low, medium, and high exposure levels, respectively. No significant results were found for officers or enlisted groundcrew.

GGTP

No significant or marginally significant results were found. A non-significant dose-response relationship was seen for enlisted flyers and officers in the continuous analyses but, conversely, a nonsignificant decreasing dose-response relationship was seen in the enlisted groundcrew.

TABLE 13-16.

Adjusted Categorical Exposure Index Analyses (Main Effects Model) Results for Hepatic Function Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	125	129	120	Overall		0.508
					M vs. L	1.60 (0.64,3.98)	0.312
					H vs. L	1.02 (0.38,2.77)	0.963
SGOT	Enlisted Flyer	55	65	57	Overall		0.108
					M vs. L	7.79 (0.77,79.20)	0.083
					H vs. L	5.38 (0.49,59.50)	0.170
	Enlisted Groundcrew	152	160	140	Overall		0.023
					M vs. L	2.14 (0.77,5.99)	0.147
					H vs. L	3.64 (1.36,9.72)	0.010
	Officer	125	129	120	Overall		0.768
					M vs. L	0.97 (0.48,1.97)	0.933
					H vs. L	0.77 (0.37,1.64)	0.504
SGPT		Enlisted	55	65	57	Overall	0.036
	Flyer				M vs. L	6.55 (1.25,34.43)	0.026
					H vs. L	4.29 (0.75,24.35)	0.101
	Enlisted Groundcrew	152	160	140	Overall		0.457
					M vs. L	1.53 (0.77,3.01)	0.223
					H vs. L	1.18 (0.57,2.48)	0.655

TABLE 13-16. (continued)

Adjusted Categorical Exposure Index Analyses (Main Effects Model) Results for Hepatic Function Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	125	129	120	Overall		0.987
					M vs. L	1.02 (0.38,2.72)	0.968
					H vs. L	0.94 (0.35,2.54)	0.906
GGTP	Enlisted Flyer	55	65	57	Overall		0.798
					M vs. L	1.51 (0.41,5.65)	0.536
					H vs. L	1.46 (0.37,5.78)	0.586
	Enlisted Groundcrew	152	160	140	Overall		0.760
					M vs. L	0.74 (0.34,1.64)	0.462
					H vs. L	0.89 (0.40,1.97)	0.776
	Officer	126	129	120	Overall		0.272
					M vs. L	2.44 (0.65,9.05)	0.184
					H vs. L	0.91 (0.19,4.36)	0.926
Alkaline Phosphatase	Enlisted Flyer	54	64	56	Overall		0.191
					M vs. L	4.84 (0.52,44.80)	0.165
					H vs. L	5.34 (0.58,49.06)	0.139
	Enlisted Groundcrew	153	160	141	Overall		0.431
					M vs. L	1.35 (0.50,3.59)	0.552
					H vs. L	1.82 (0.72,4.59)	0.202

TABLE 13-16. (continued)

Adjusted Categorical Exposure Index Analyses (Main Effects Model) Results for Hepatic Function Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Total Bilirubin	Officer	125	129	120	Overall		0.851
					M vs. L	0.67 (0.10,4.51)	0.677
					H vs. L	1.10 (0.18,6.61)	0.915
	Enlisted Flyer[a]	54	65	57	--	--	--
	Enlisted Groundcrew	152	160	140	Overall		0.332
					M vs. L	0.41 (0.10,1.65)	0.208
					H vs. L	1.02 (0.32,3.23)	0.971
Direct Bilirubin	Officer	125	129	120	Overall		0.354
					M vs. L	2.69 (0.46,15.82)	0.274
					H vs. L	3.10 (0.56,17.25)	0.196
	Enlisted Flyer	55	65	57	Overall		0.466
					M vs. L	2.97 (0.48,18.38)	0.241
					H vs. L	1.79 (0.24,13.43)	0.571
	Enlisted Groundcrew	152	160	140	Overall		0.767
					M vs. L	1.61 (0.43,6.06)	0.480
					H vs. L	1.40 (0.36,5.51)	0.628

TABLE 13-16. (continued)

Adjusted Categorical Exposure Index Analyses (Main Effects Model) Results for Hepatic Function Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Cholesterol	Officer	125	129	120	Overall		0.107
					M vs. L	0.54 (0.27,1.09)	0.085
					H vs. L	0.50 (0.25,1.03)	0.060
	Enlisted Flyer	55	65	57	Overall		0.972
					M vs. L	1.02 (0.38,2.73)	0.962
					H vs. L	1.12 (0.42,3.02)	0.822
	Enlisted Groundcrew	152	160	140	Overall		0.417
					M vs. L	1.20 (0.57,2.55)	0.630
					H vs. L	1.61 (0.78,3.30)	0.194
Triglycerides	Officer	125	129	120	Overall		0.721
					M vs. L	0.97 (0.38,2.45)	0.946
					H vs. L	1.35 (0.55,3.32)	0.514
	Enlisted Flyer	55	65	57	Overall		0.379
					M vs. L	2.66 (0.62,11.39)	0.189
					H vs. L	2.06 (0.44,9.60)	0.358
	Enlisted Groundcrew	152	160	140	Overall		0.363
					M vs. L	0.44 (0.14,1.42)	0.173
					H vs. L	0.60 (0.19,1.86)	0.375

[a]No analysis done since there were only three abnormal (one medium, two high).

TABLE 13-17.

Adjusted Continuous Exposure Index Analyses (Main Effects Model) for Hepatic Function Variables and Two Porphyrin Determinations by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
SGOT	Officer	n	125	129	120	Overall	0.718
		Adj. Mean	33.6	34.7	33.8	M vs. L	0.450
						H vs. L	0.904
	Enlisted Flyer	n	55	65	57	Overall	0.276
		Adj. Mean	30.3	32.8	32.7	M vs. L	0.144
						H vs. L	0.184
	Enlisted Groundcrew	n	152	160	140	Overall	0.409
		Adj. Mean	33.5	34.1	35.0	M vs. L	0.595
						H vs. L	0.183
SGPT	Officer	n	125	129	120	Overall	0.695
		Adj. Mean	20.1	20.0	19.1	M vs. L	0.969
						H vs. L	0.451
	Enlisted Flyer	n	55	65	57	Overall	0.058
		Adj. Mean	18.1	21.4	21.8	M vs. L	0.047
						H vs. L	0.030
	Enlisted Groundcrew	n	152	160	140	Overall	0.581
		Adj. Mean	20.2	21.4	21.0	M vs. L	0.309
						H vs. L	0.492