TABLE 13-17. (continued)

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
	Officer	n	125	129	120	Overall	0.828
		Adj. Mean	30.9	32.2	32.4	M vs. L	0.611
						H vs. L	0.580
GGTP	Enlisted	n	55	65	57	Overall	0.286
	Flyer	Adj. Mean	36.6	42.6	44.6	M vs. L	0.230
						H vs. L	0.132
	Enlisted	n	152	160	140	Overall	0.299
	Groundcrew	Adj. Mean	36.9	36.6	33.1	M vs. L	0.914
						H vs. L	0.159
	Officer	n	126	129	120	Overall	0.843
		Adj. Mean	82.3	82.9	83.8	M vs. L	0.808
						H vs. L	0.561
Alkaline Phosphatase	Enlisted	n	54	64	56	Overall	0.127
	Flyer	Adj. Mean	90.7	99.3	97.7	M vs. L	0.053
						H vs. L	0.122
	Enlisted	n	153	160	141	Overall	0.576
	Groundcrew	Adj. Mean	91.5	94.0	93.5	M vs. L	0.318
						H vs. L	0.444

TABLE 13-17. (continued)

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
Total Bilirubin	Officer	n	125	129	120	Overall	0.439
		Adj. Mean	0.77	0.75	0.79	M vs. L	0.504
						H vs. L	0.545
	Enlisted Flyer	n	55	65	57	Overall	0.070
		Adj. Mean	0.69	0.76	0.79	M vs. L	0.128
						H vs. L	0.023
	Enlisted Groundcrew	n	152	160	140	Overall	0.240
		Adj. Mean	0.73	0.74	0.78	M vs. L	0.838
						H vs. L	0.117
Direct Bilirubin	Officer	n	125	129	120	Overall	0.567
		Adj. Mean	0.20	0.19	0.21	M vs. L	0.517
						H vs. L	0.689
	Enlisted Flyer	n	55	65	57	Overall	0.724
		Adj. Mean	0.18	0.19	0.19	M vs. L	0.471
						H vs. L	0.498
	Enlisted Groundcrew	n	152	160	140	Overall	0.550
		Adj. Mean	0.17	0.19	0.18	M vs. L	0.277
						H vs. L	0.670

TABLE 13-17. (continued)

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
LDH	Officer	n	125	129	120	Overall	0.232
		Adj. Mean	134.0	131.3	128.9	M vs. L	0.373
						H vs. L	0.088
	Enlisted Flyer	n	55	65	57	Overall	0.101
		Adj. Mean	114.4	112.4	120.9	M vs. L	0.619
						H vs. L	0.129
	Enlisted Groundcrew	n	152	160	140	Overall	0.092
		Adj. Mean	125.3	125.3	129.7	M vs. L	0.997
						H vs. L	0.055
Cholesterol	Officer	n	125	129	120	Overall	0.049
		Adj. Mean	236.7	225.0	224.2	M vs. L	0.039
						H vs. L	0.029
	Enlisted Flyer	n	55	65	57	Overall	0.214
		Adj. Mean	213.2	208.1	220.6	M vs. L	0.492
						H vs. L	0.343
	Enlisted Groundcrew	n	152	160	140	Overall	0.945
		Adj. Mean	209.6	211.1	210.1	M vs. L	0.742
						H vs. L	0.927

TABLE 13-17. (continued)

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
Triglycerides	Officer	n	125	129	120	Overall	0.739
		Adj. Mean	110.0	108.5	116.3	M vs. L	0.886
						H vs. L	0.558
	Enlisted Flyer	n	55	65	57	Overall	0.981
		Adj. Mean	112.5	111.2	113.7	M vs. L	0.919
						H vs. L	0.927
	Enlisted Groundcrew	n	152	160	140	Overall	0.922
		Adj. Mean	110.9	109.9	107.9	M vs. L	0.890
						H vs. L	0.690
Uroporphyrin	Officer	n	125	129	120	Overall	0.856
		Adj. Mean	17.49	16.69	17.45	M vs. L	0.621
						H vs. L	0.977
	Enlisted Flyer	n	54	65	57	Overall	0.703
		Adj. Mean	18.58	16.96	18.27	M vs. L	0.438
						H vs. L	0.890
	Enlisted Groundcrew	n	151	160	139	Overall	0.644
		Adj. Mean	16.39	16.54	15.45	M vs. L	0.903
						H vs. L	0.451

TABLE 13-17. (continued)

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
	Officer	n	125	129	120	Overall	0.901
		Adj. Mean	127.65	128.84	130.26	M vs. L	0.833
						H vs. L	0.649
Coproporphyrin	Enlisted Flyer	n	55	65	57	Overall	0.669
		Adj. Mean	108.67	115.31	109.81	M vs. L	0.408
						H vs. L	0.890
	Enlisted Groundcrew	n	151	160	140	Overall	0.325
		Adj. Mean	115.28	115.71	122.88	M vs. L	0.935
						H vs. L	0.177

Alkaline Phosphatase

For the enlisted groundcrew and the enlisted flyers, the lowest abnormal prevalence rate and lowest mean value were found in the low exposure category. A nonsignificant increasing dose-response relationship was seen within these occupations for the discrete analyses. In both unadjusted and adjusted continuous analyses, a marginally significant medium versus low contrast was found for enlisted flyers ($p=0.086$ and $p=0.053$, respectively), with unadjusted means of 88.9 U/L, 96.3 U/L, and 95.2 U/L for the low, medium, and high exposure levels, respectively.

Total Bilirubin

Discrete analyses revealed no significant findings; adjusted discrete analyses for enlisted flyers were not done due to sparse data. Continuous analyses revealed a significant overall effect ($p=0.045$, unadjusted) for enlisted flyers, which was marginally significant after adjustment ($p=0.070$). In both unadjusted and adjusted analyses, the high versus low mean contrast was significant ($p=0.014$ and $p=0.023$, respectively), with unadjusted means of 0.66 mg/dl, 0.73 mg/dl, and 0.76 mg/dl for the low, medium, and high exposure levels, respectively.

Direct Bilirubin

There were no significant exposure findings in either the continuous or discrete analyses, although within each occupational cohort, the lowest abnormal prevalence rate was found in the low exposure group.

LDH

The unadjusted discrete analyses revealed no significant or marginally significant results. No adjusted discrete analyses were done due to sparse data. The unadjusted continuous analyses for the enlisted groundcrew showed a significant overall relationship with the exposure index ($p=0.031$), with mean values of 123.1 U/L, 122.3 U/L, 127.9 U/L for the low, medium, and high exposure levels; the high versus low contrast was significant ($p=0.037$). After adjustment, the continuous analyses for enlisted groundcrew revealed marginally significant results ($p=0.092$, overall; $p=0.055$, high versus low). No significant or marginally significant results were seen for enlisted flyers or officers. Enlisted flyers and enlisted groundcrew had the largest mean values for their highest exposure category, which is reversed in the officers, who exhibited a nonsignificant decreasing dose-response relationship with exposure level.

Cholesterol

Significant or marginally significant results were found for officers in the direction of a decreasing dose-response relationship in both the adjusted continuous (overall $p=0.049$, medium versus low $p=0.039$, high versus low $p=0.029$) and adjusted discrete (medium versus low $p=0.085$, high versus low $p=0.060$) analyses. Neither of the enlisted cohorts demonstrated a similar decreasing response.

Triglycerides

No significant or marginally significant results were found.

Uroporphyrins and Coproporphyrins

No significant or marginally significant results were found.

EXPOSURE INDEX ANALYSES

Additional continuous analyses were done to examine pairwise interactions involving exposure level and the covariates. Ten exposure group-by-covariate interactions were found at $p \leq 0.05$. All interactions were found in the enlisted flyer and enlisted groundcrew occupations. Eight of the interactions involved current alcohol consumption, one involved age, and one involved race. The interactions are summarized in Tables K-5 and K-6 of Appendix K. In Table K-5 of Appendix K, the slope of the continuous covariate with respect to the dependent variable is provided for each of the three exposure levels. Table K-6 of Appendix K presents the mean level of direct bilirubin for each of the three exposure levels by race. The interactions involving current alcohol consumption are mainly due to a nonsignificant dependent variable response to increasing alcohol consumption in the low exposure group in contrast to a significant positive response for the medium and high groups. The SGOT, SGPT, and GGTP interaction results for the enlisted groundcrew provide support for an interpretation of herbicide effect.

In summary, the nine hepatic function variables and two porphyrin metabolite variables showed no conclusive evidence of a dose-response relationship at the followup examination. Five overall exposure group differences were found. Only two of these (SGOT for enlisted groundcrew, and total bilirubin for enlisted flyers) supported a dose-response relationship.

LONGITUDINAL ANALYSES

Three hepatic enzyme variables, SGOT, SGPT, and GGTP, were chosen for longitudinal analysis, spanning the spectrum of intermediate to acute effects. These test variables were chosen because both the Baseline and the followup assays were performed by the high-precision ACA 500® DuPont technology. The data from these three hepatic variables are arrayed in Table 13-18.

The SGOT and SGPT data showed slight but uniform increases from the Baseline examination. These increases were proportionately the same for both the Ranch Hand and Comparison groups. These changes may reflect an aging effect or are due to laboratory variation. As indicated by the equality-of-difference p-values, none of the three hepatic variables showed a statistically significant difference in the changes from Baseline to followup between groups.

TABLE 13-18.

Longitudinal Analyses for SGOT, SGPT, and GGTP:
A Contrast of Baseline and First Followup Examination Test Means

Variable	Group	Total	Means 1982 Baseline	Means 1985 Followup	p-Value* (Equality of Difference)
SGOT	Ranch Hand	971	32.91	33.73	0.61
	Comparison	1,139	32.97	33.73	
SGPT	Ranch Hand	971	20.08	21.82	0.72
	Comparison	1,139	20.51	22.44	
GGTP	Ranch Hand	971	39.26	33.16	0.63
	Comparison	1,139	38.64	32.35	

*Analyzed in log units.

SUMMARY AND CONCLUSIONS

The interval questionnaire revealed sparse reporting of liver disorders from 1982 to 1985 that was not significantly different between groups. Historical liver disease was verified by medical records, and these data were added to the verified Baseline history to assess possible lifetime differences. No significant differences were found. The medical record verification process showed that the historical data were generally correctly reported and classified between groups, except for the category of enlarged liver which showed a higher verification rate in the Comparison group.

Digestive system mortality showed an overall nonsignificant excess in the Ranch Hands, but a relative nonsignificant excess of malignant neoplasms in the Comparisons.

No differences were found for past or current peptic ulcer disease for the Ranch Hand and Comparison groups, adjusted for standard covariates as well as blood type.

The physical examination disclosed a borderline significant increase of hepatomegaly in the Ranch Hand group. Emphasis was placed on nine laboratory test variables measuring liver function, i.e., serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), gamma-glutamyl transpeptidase (GGTP), alkaline phosphatase, total and direct bilirubin, lactic dehydrogenase (LDH), cholesterol, and triglycerides. In addition, uroporphyrin and coproporphyrin measurements were obtained to assess liver function and the likelihood of porphyria cutanea tarda (PCT). The nine hepatic variables were subjected to continuous and categorical statistical tests, and were adjusted for the covariates age, race, occupation, current alcohol consumption, and unprotected exposure to both industrial chemicals and degreasing chemicals. Final statistical models used only

the significant covariates and two-way interactions for adjustment. The two porphyrin measurements were analyzed only in the continuous form. The overall summary results of the analyses of these 11 variables are given in Table 13-19.

The results showed a significantly lower mean SGPT level, a greater mean alkaline phosphatase level, a lower mean uroporphyrin level for Ranch Hands as contrasted with Comparisons, and a marginally significant greater mean coproporphyrin level. Only in the instance of alkaline phosphatase did the discrete analysis approach statistical significance. No group differences were noted for SGOT, GGTP, total and direct bilirubin, LDH, cholesterol, or triglycerides. However, an analysis using only the Original Comparisons revealed a significantly greater mean cholesterol level in the Comparison group. A review of the covariate effects in the adjusted statistical models revealed that all covariates behaved as expected with the exception of alcohol consumption for the alkaline phosphatase analysis, which showed an inverse relationship with wine consumption.

Exploration of group-by-group covariate interactions for alkaline phosphatase, direct bilirubin, triglycerides, SGOT, and uroporphyrins revealed significant group differences within specific covariate strata. In particular, Ranch Hands exposed to industrial chemicals had a significantly higher adjusted mean level of alkaline phosphatase and a significantly higher abnormal prevalence rate of direct bilirubin than similarly exposed Comparisons. For triglycerides, Ranch Hands born in or before 1922 had a significantly higher adjusted mean level than similar aged Comparisons, while Ranch Hand officers exhibited a significantly higher abnormal prevalence rate than Comparison officers. For SGOT, Ranch Hand moderate current drinkers (more than one to four drinks per day) had a significantly higher mean level than corresponding Comparisons. In the opposite direction, Comparisons with a mean BUN level less than or equal to 14 (median for all participants) were found to have a significantly higher adjusted mean uroporphyrin level than similar Ranch Hands. These results did not disclose any common pattern detrimental to the Ranch Hand group.

These findings were generally consistent with the 1982 Baseline data, which disclosed a significantly increased mean cholesterol level in the Comparisons and nonsignificant Ranch Hand mean elevations for GGTP and LDH. Slight differences in analytic results are probably due to the use of more fully adjusted models used for the followup examination data.

Overall, the followup examination laboratory data showed no adverse clinical or exposure patterns in either group. Further, the detection of significant mean shifts (still within normal range) by the continuous statistical tests, not mirrored by the categorical tests, suggests a circumstance of statistical power rather than findings of biological relevance.

Of the five significant or marginally significant results that were found in the adjusted exposure index analyses, four exhibited a trend suggestive of an increasing dose-response relationship. In the enlisted flyer cohort, the percentages of SGPT abormalities were significantly different and increased from the low to the high exposure categories. The corresponding mean values were marginally significantly different among exposure levels. Also, the mean levels of total bilirubin were marginally significantly different among exposure levels, increasing with exposure level. For enlisted groundcrew, the percentage of SGOT abnormalities significantly differed among

TABLE 13-19.

Overall Summary Results of Unadjusted and Adjusted Analyses of Nine Hepatic Function Variables and Two Porphyrin Metabolite Tests

Variable	Unadjusted		Adjusted*			Direction of Results**
	Mean	Categorical	Mean CC	Mean CD	Categorical DD	
Questionnaire						
Liver Disease (Lifetime History)						
Hepatitis	--	NS	--	--	--	
Jaundice	--	NS	--	--	--	
Cirrhosis	--	NS	--	--	--	
Enlarged Liver	--	NS	--	--	--	
Miscellaneous Liver Disorders	--	NS	--	--	--	
Peptic Ulcer Disease	--	NS	--	--	NS[a]	
Physical Examination						
Hepatomegaly	--	NS*	--	--	--	RH>C
Laboratory Testing						
SGOT	NS	NS	NS	****	NS	
SGPT	NS*	NS	0.048	0.029	NS	C>RH
GGTP	NS	NS	NS	NS	NS	
Alkaline Phosphate	0.009	NS	0.008	****	NS*	RH>C
Total Bilirubin	NS	NS	NS	NS	NS	
Direct Bilirubin	NS	NS	NS	NS	****	
LDH	NS	NS	****	NS	NS	
Cholesterol	NS	NS	NS	NS	NS	
Triglycerides	NS	NS	****	NS	****	
Uroporphyrin	0.048	--	****	--	--	C>RH
Coproporphyrin	NS*	--	NS*	--	--	RH>C
Questionnaire-Laboratory Correlation						
Skin Bruises, Patches, and Sensitivity	--	0.001	--	--	--	RH>C

*C: Continuous
D: Discrete
**RH>C: more abnormalities, or higher mean value, in Ranch Hands.
C>RH: more abnormalities, or higher mean value, in Comparisons.
[a]Adjusted for blood type.
NS: Not significant ($p>0.10$).
NS*: Borderline significant ($0.05<p\leq0.10$).
--Analysis not performed.
****Group-by-covariate interaction.

exposure levels. Within the enlisted flyer cohort, all nine laboratory tests of hepatic function had the lowest percentage of abnormalities in the low exposure category; correspondingly, six of the nine mean levels were lowest for the low exposure category. Of the ten group-by-covariate interactions that were found, three (SGOT, SGPT, and GGTP) supported a dose-response relationship in the enlisted groundcrew cohort. Exploration of these interactions revealed a trend that showed an increasing association between current alcohol consumption and the dependent variables for increasing exposure levels.

Longitudinal analyses for SGOT, SGPT, and GGTP disclosed no statistically significant group differences in the mean shifts from the Baseline to the followup examination.

Interval reporting of PCT-like symptoms of skin patches, bruises, and sensitivity was significantly increased in the Ranch Hands ($p=0.001$). However, when these historic data were contrasted to both uroporphyrin and coproporphyrin abnormalities, no correlation was apparent, nor were there any significant group differences. Since an elevation in the uroporphyrin level is required for a diagnosis of PCT, the historic data were retabulated with only uroporphyrin abnormalities; again, no group differences were apparent, and, in fact, uroporphyrin abnormalities in both groups were higher in those participants without a history of skin disorders than in those participants with such a history. The likelihood of bona fide PCT among study participants, and particularly among the Ranch Hands, appears to be remote.

In conclusion, the followup examination disclosed more statistically significant findings for tests of liver function than the Baseline examination, but they were equally divided between the two groups and did not demonstrate clinical, statistical, or exposure patterns consistent with an herbicide-related effect on health. No evidence was found to suggest an increased likelihood of PCT among the Ranch Hand group.

CHAPTER 13

REFERENCES

1. Kimbrough, R.D., C.D. Carter, J.A. Liddle, R.E. Cline, and P.E. Phillips. 1977. Epidemiology and pathology of a tetrachlorodibenzodioxin poisoning episode. Arch. Environ. Health 32(2):7-86.

2. McNulty, W.P. 1977. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin for Rhesus monkeys: Brief report. Bull. Environ. Contam. Toxicol. 18(1):108-109.

3. Olson, J.R., M.A. Holscher, and R.A. Neal. 1980. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the golden Syrian hamster. Toxicol. Appl. Pharmacol. 55:67-78.

4. Palmer, J.S., and R.D. Radeleff. 1964. The toxicologic effects of certain fungicides and herbicides on sheep and cattle. Ann. N.Y. Acad. Sci. 11:729-736.

5. Goldstein, J.A., P. Hickman, H. Bergman, and J.G. Vos. 1973. Hepatic porphyria induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in the mouse. Res. Commun. Chem. Pathol. Pharmacol. 6:919.

6. Madhukar, B.V., and F. Matsumura. 1981. Difference in the nature of induction of mixed-function oxidase systems of the rat liver among phenobarbital, DDT, 3-methylcholanthrene, and TCDD. Toxicol. Appl. Pharmacol. 61:110-118.

7. Kohli, K.K., and J.A. Goldstein. 1981. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on hepatic and renal prostaglandin synthetase. Life Sci. 19:299-305.

8. Thunberg, T., and H. Hakansson. 1983. Vitamin A (retinol) status in the Gunn rat: The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Arch. Toxicol. 53:225-234.

9. Goldstein, J.A., P. Hickman, and D.L. Jue. 1974. Experimental hepatic porphyria induced by polychlorinated biphenyls. Toxicol. Appl. Pharmacol. 27:437.

10. Sassa, S., H. De Verneuil, and A. Kappas. 1984. Inhibition of uroporphyrinogen decarboxylase activity in polyhalogenated aromatic hydrocarbon poisoning. In Banbury report 18: Biological mechanisms of dioxin action, ed. A. Poland and R.D. Kimbrough, pp. 215-222. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory.

11. Sweeney, G., D. Basford, B. Rowley, and G. Goddard. 1984. Mechanisms underlying the hepatotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin. In Banbury report 18: Biological mechanisms of dioxin action, ed. A. Poland and R.D. Kimbrough, pp. 255-239. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory.

12. Greig, J. 1984. Differences between skin and liver toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mice. In Banbury report 18: Biological mechanisms of dioxin action, ed. A. Poland and R.D. Kimbrough, pp. 391-397. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory.

13. Goldmann, 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-tetrachlorodibenzo-dioxin). Der Hautarzt. 24(4):149-152.

14. Oliver, R.M. 1975. Toxic effects of 2,3,7,8-tetrachlorodibenzo 1,4-dioxin in laboratory workers. Br. J. Ind. Med. 32:49-53.

15. Reggiani, G. 1980. Acute human exposure to TCDD in Seveso, Italy. J. Toxicol. Environ. Health 6:27-43.

16. Reggiani, G. 1979. Estimation of the TCDD toxic potential in the light of the Seveso accident. Arch. Toxicol. 2:291-302.

17. Suskind, R.R. 1978. 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 11, 1978. 7 pp.

18. May, G. 1982. Tetrachlorodibenzodioxin: A survey of subjects ten years after exposure. Br. J. Ind. Med. 39:128-135.

19. Ideo, G., G. Bellati, A. Bellobuono, A. Mocarelli, P. Marocchi, A. and P. Brambilla. 1982. Increased urinary d-glucaric acid excretion by children living in an area polluted with tetrachlorodibenzodioxin (TCDD). Clin. Chem. Acta. 120:273-283.

20. May, G. 1973. Chlorance from the accidental production of tetrachloro-dibenzodioxin. Br. J. Ind. Med. 30:276-283.

21. 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.

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

23. 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.

24. Martin, J.V. 1984. Lipid abnormalities in workers exposed to dioxin. Br. J. Ind. Med. 41:254-256.

25. 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.

26. 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.

27. Bleiberg, J., M. Wallen, R. Brodkin, and I.L. Applebaum. 1964. Industrially acquired porphyria. Arch. Dermatol. 89:793-797.

28. 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.

29. 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 tarda, and psychologic parameters. Arch. Environ. Health 22(3):316-327.

30. Peters, H.A., A. Gocmen, D.J. Cripps, G.T. Bryan, and I. Dogramaci. 1982. Epidemiology of hexachlorobenzene-induced porphyria in Turkey. Arch. Neurol. 39:744-749.

31. Rubenstein, E., and D.D. Federman, eds. 1986. Metabolism: The porphyrias. Chap. 9 in Scientific American Medicine. New York: Scientific American, Inc.

CHAPTER 14

DERMATOLOGICAL EVALUATION

INTRODUCTION

The skin is a major target organ following heavy exposure to chlorophenols and dioxin and, therefore, is a primary focus of the AFHS clinical examination.

Since the association between chlorinated chemicals and chloracne was first noted in 1957,[1,2] a variety of animal experiments have shown the dermal sensitivity of rabbits, monkeys, and hairless mice to TCDD, 2,4,5-T (contaminated with TCDD), and other chlorinated dibenzo compounds, furans, or their brominated analogs.[1-7] Chloracne is not associated with exposure to 2,4-D.[8] Accidental exposure to waste oils containing TCDD has caused significant dermal symptoms, including loss of hair, ulcerative dermatitis, and inflamed mucous membranes in horses, dogs, cats, and mice.[9,10] Studies have suggested that the chloracnegens induce a series of pathological skin changes in target cells of the epithelial lining of sebaceous glands via the Ah receptor.[11] Hyperkeratinization of these cells eventually leads to the formation of the comedone characteristic of acne.

In humans, development of the hallmark rash, chloracne, is generally acknowledged to represent substantial topical or systemic exposure to one or more chloracnegens.[1,5,6,12-18] Acute fulminant chloracne is characterized by a maculopapular rash of active comedones, conforming to an eyeglass or facial butterfly distribution, often accompanied by chest, back, or eyelid lesions.[5,18]

The severity of the chloracne appears to be generally dose related, but may also depend on the route of administration, age, genetic predisposition, and/or the existence of acne vulgaris or other skin disorders.[5,15,18] Occasionally, exposure, via contaminated clothes of an industrial worker, has been associated with chloracne in family members.[19] Sequelae from severe chloracne include actinic elastosis, acne scars, disfigurement, excessive hair growth, and Peyronie's disease.[5,16] Severe chloracne is often accompanied by acute effects in other organ systems. In contrast, low to moderate exposure to chloracnegens generally produces mild chloracne with few, if any, attendant systemic signs and symptoms.

The clinical diagnosis of acute chloracne is easier than the diagnosis of subacute and chronic chloracne. In the latter instances, a history of exposure to chloracnegens is essential in the diagnosis, particularly if the individual has experienced adolescent acne. Chronic chloracne has been clinically observed more than 30 years after onset,[16] but a biopsy is often necessary to confirm these cases.[18] Mild or transient cases of chloracne may be confused with persistent adolescent acne or other skin conditions.

As noted in the AFHS Baseline Morbidity Report, over one-half of the veteran complaints in the Veterans Administration Herbicide Registry involved dermatological conditions, a fact sometimes alluded to as "evidence" of exposure to Agent Orange. In actuality, skin disease was a major medical problem among American troops serving in Vietnam. Forty-seven percent of the combat-days lost in the 9th Infantry Division from July 1968 to June 1969 were due to dermatological conditions.[19] These diseases were directly related to the tropical climate and terrain. Only in rare cases has the Veterans Administration made a diagnosis of chloracne in a Vietnam combat veteran. The natural history of chloracne suggests that most cases should have been diagnosed while in Vietnam, but a dermatological survey failed to reveal any cases.[20]

Most recognized chloracne cases have been diagnosed in chemical plant workers or in victims of industrial accidents. Thousands of cases were recorded in the 1930-1940 era, and earlier descriptions of chloracne-like disease were found in 1897 to 1901.[21] Industrial exposure to chloracnegens has been generally characterized as moderate-prolonged or severe-acute. In the setting of casual-sporadic exposure, as in the typical cases of the contaminated housing areas in Times Beach, Missouri, and the Quail Run Trailer Park, chloracne is virtually unknown.[22,23]

A number of dioxin morbidity studies have shown a clustering of abnormal laboratory tests in individuals with chloracne.[13,15-17,24-27] This has led some investigators to believe that long-term sequelae to dioxin exposure will be found only in people with chloracne.[16] Other investigators feel that this belief is not consistent with normal spectrum-of-illness concepts and that effects may occur in the absence of chloracne.[28]

Baseline Summary Results

The 1982 Baseline clinical examination revealed an unexpected significant excess ($p=0.03$) of basal cell carcinoma in the Ranch Hand group. Risk factor data (e.g., sun exposure, host factors of tannability, complexion) were not collected in 1982.

The 1982 examination focused on the diagnosis of chloracne both in historical terms by a detailed questionnaire and in contemporary terms via a comprehensive clinical assessment. The questionnaire data did not demonstrate anatomic, incidence, or onset-time patterns of acne in the Ranch Hand group that might support an inference of past chloracne, nor did the physical examination detect a single case. Fourteen biopsies from 11 participants also failed to document a chloracne diagnosis. A dermatology index (the number of clinically detected skin abnormalities per individual) was virtually identical between the Ranch Hand and Comparison groups, and was associated with the history of past acne in both groups. No exposure level associations were noted in any occupational category of the Ranch Hand group. The comprehensive dermatological assessment did not reveal evidence of past or current chloracne in the Ranch Hand group.

Parameters of the 1985 Dermatological Evaluation

Questionnaire data recaptured many of the acne parameters of the 1982 questionnaire, and the physical examination parameters were similar to the

1982 Baseline examination. Particular emphasis was given to the diagnosis of basal cell carcinoma and to the collection of risk factor data, e.g., skin color, reaction to sun, ethnicity (see Chapter 10, Malignancy).

Thus, the dependent variables and covariates of the analyses below closely approximated those previously conducted on the Baseline examination and questionnaire data. The adjusted statistical analyses were based on logistic regression (BMDP®-LR) and log-linear models (BMDP®-4F), and the unadjusted analyses primarily use Pearson's chi-square test and Fisher's exact test. In addition, an empiric Venn diagram was used to explore the potential of historic chloracne. Parallel analyses using only Original Comparisons are presented in Tables L-3 through L-11 of Appendix L.

RESULTS AND DISCUSSION

General

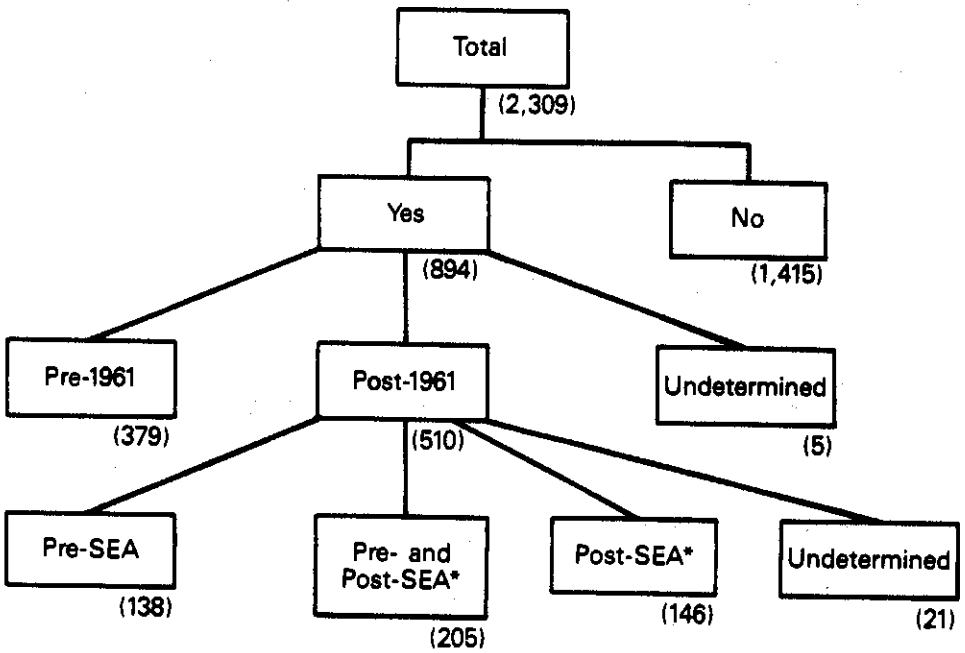
Detailed dermatological data were obtained by standard physical examination techniques. Numeric differences in summary tables reflect missing dependent variable and undeterminable covariate information. One participant refused the dermatology examination; consequently, all skin disorder analyses were based on 2,308 participants. Data were collected on 22 skin disorders, which were in turn reduced to eight variables for analysis: comedones, acneiform lesions, acneiform scars, depigmentation, inclusion cysts, hyperpigmentation, other abnormalities, and the dermatology index. Descriptions of skin biopsies, which were also conducted at the physical examination, are given in this chapter. Followup questionnaire information regarding the presence, time, and location of acne was also analyzed. The analyses in this chapter first investigate questionnaire information on acne, and subsequent analyses center upon the eight skin disorder variables and the skin biopsies.

Four covariates were included in this analysis: age, race, occupation, and presence of acne before duty in Southeast Asia. Age is used in its continuous form for all adjusted logistic regression analyses, but age is trichotomized (born in 1942 or after, born between 1923 and 1941, and born in 1922 or before) for presentation in summary tables and for use in dependent variable and covariate association analyses and log-linear models. Participants were categorized as either Black or nonblack. Occupation was divided into the three classifications of officer, enlisted flyer, and enlisted groundcrew. Sample size differences in subsequent adjusted analyses reflect missing dependent variable data or missing data on the presence of acne before duty in Southeast Asia.

Questionnaire Data

The acne status of each participant was determined by Baseline and followup questionnaire information. In particular, the occurrence of acne and the dates for acne occurrence have been determined and analyzed. Additionally, the analysis of the location of acne is presented for a subset of the participants who have had acne.

Figure 14-1 below is a diagram explaining the occurrence of acne by time determination for the 2,309 participants, along with frequencies and an explanation of terms.



Yes to Acne — Reported acne on both/either Baseline and/or followup study.

No to Acne — Never had acne.

Pre-1961 Acne — Participants with acne who had last occurrence of acne in or before 1961.

Post-1961 Acne — Participants with acne who had an occurrence of acne sometime after 1961.

Undetermined — Time reference not determinable from date information available.

Pre-SEA Acne — Participants with post-1961 acne who had all occurrences of acne before the start of first Southeast Asia (SEA) tour (as determined from military records).

Post-SEA Acne — Participants with post-1961 acne who had all occurrences of acne after the start of first SEA tour.

Pre- and Post-SEA Acne — Participants with post-1961 acne who had multiple occurrences, both before and after the start of first SEA tour, or a case of acne that began before the start of first SEA tour and that ended after starting SEA tour.

*: Analysis of location of acne performed for these participants.

Figure 14-1.
Occurrence of Acne by Time for First Followup Participants

The distinction was made between pre-1961 and post-1961, since herbicide missions in Vietnam commenced in 1962. Responses of 2,309 participants indicated that 1,415 individuals never had acne, 379 had acne before 1961, 138 had acne after 1961 but before duty in SEA, 205 had acne both before and after duty in SEA, 146 had acne only after SEA duty, and 26 participants could not be specifically classified.

Occurrence of Acne

The reported occurrence of acne, as determined by Baseline and followup questionnaires, is displayed in Table 14-1. The analysis showed that the Ranch Hand group reported slightly more acne than the Comparison group, although the difference is nonsignificant (p=0.111). Analyses using Original Comparisons only showed a borderline significance (p=0.071) found in Table L-3 of Appendix L.

The participants who responded "yes" to acne were categorized according to whether their acne occurred before or after 1961. The distribution of pre-1961 versus post-1961 acne is given in Table 14-2.

TABLE 14-1.

Unadjusted Analysis for Reported Historical Occurrence of Acne by Group

	Acne					
	Yes		No			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	412	40.6	604	59.4	1,016	Est. RR: 1.15
Comparison	482	37.3	811	62.7	1,293	95% C.I.: (0.97,1.36)
						p-Value: 0.111
Total	894		1,415		2,309	

TABLE 14-2.

Unadjusted Analysis for Reported Historical Occurrence of Acne Relative to 1961 by Group*

Group	Occurrence of Acne				Total	Summary Statistics
	Post-1961		Pre-1961			
	Number	Percent	Number	Percent		
Ranch Hand	239	58.3	171	41.7	410	Est. RR: (for post-1961 cases): 1.07 95% C.I.: (0.82, 1.04) p-Value: 0.634
Comparison	271	56.6	208	43.4	479	
Total	510		379		889	

*Five participants deleted due to missing data at time of occurrence.

As shown, no significant difference in the distribution of post-1961 versus pre-1961 acne existed between Ranch Hands and Comparisons (p=0.634).

Cases of post-1961 acne were classified to SEA tour(s) of duty, as determined by military records. The distribution of post-1961 acne cases relative to SEA is shown in Table 14-3.

This marginal significance (p=0.058) was due primarily to a larger percentage of Ranch Hands in the post-SEA category, as contrasted with the Comparisons (35.1% versus 25.3%).

Duration of Acne

The approximate duration of acne was examined among the three SEA categories by group using a two-factor analysis of variance. The calculation of acne duration for participants with multiple occurrences in overlapping time periods counted time periods only once. A square root transformation was used to normalize the duration data. Results from duration of acne analyses are given in Table 14-4.

TABLE 14-3.

Unadjusted Analysis for Reported Historical Occurrence of Acne Relative to SEA Tour of Duty for Post-1961 Acne by Group*

	Post-1961 Acne							
	Pre-SEA		Post-SEA		Pre- and Post-SEA			
Group	Number	Percent	Number	Percent	Number	Percent	Total	p-Value
Ranch Hand	58	25.4	80	35.1	90	39.5	228	0.058
Comparison	80	30.7	66	25.3	115	44.1	261	
Total	138		146		205		489	

*Twenty-one post-1961 participants with acne deleted due to missing data on time of occurrence.

TABLE 14-4.

Adjusted Analysis for Duration of Acne (in Years) for Post-1961 Acne by Group*

Group	Total	Adjusted Mean**	95% C.I.**	p-Value	Covariate Remarks
Ranch Hand	219	8.18	(7.43,8.96)	0.189	Time Reference to SEA ($p<0.001$)
Comparison	252	7.49	(6.82,8.19)		
Total	471				

*Eighteen participants deleted due to missing data on time of occurrence.
**Converted from square root scale.

This adjusted analysis showed no significant effect due to group ($p=0.189$), but a highly significant effect due to SEA category ($p<0.001$), with the pre- and post-SEA category having higher mean durations than the pre-SEA or post-SEA categories, which were nearly identical. No interaction was present between group and SEA category ($p=0.314$). A categorical analysis was performed, in which duration was categorized into 5-year increments (five duration categories, the last being greater than 20 years). There was no significant difference between groups (pre-SEA, $p=0.520$; post-SEA, $p=0.776$; pre- and post-SEA, $p=0.880$).

Location of Acne

The location of acne for participants classified as post-SEA or pre- and post-SEA (351 participants) was analyzed. Spatial distribution of acne with

primary emphasis on acne on the temples, around the eyes, or on the ears was determined from the questionnaire; these data are presented in Figures 14-2 and 14-3. Figure 14-2 shows the distribution of acne for Ranch Hands and Comparisons, for post-SEA and pre- and post-SEA participants combined, whereas Figure 14-3 represents a similar distribution for only post-SEA participants. If more than one episode of acne occurred, cases involving the temples, eyes, or ears took precedence. Also, multiple-site involvement took precedence over single-site involvement.

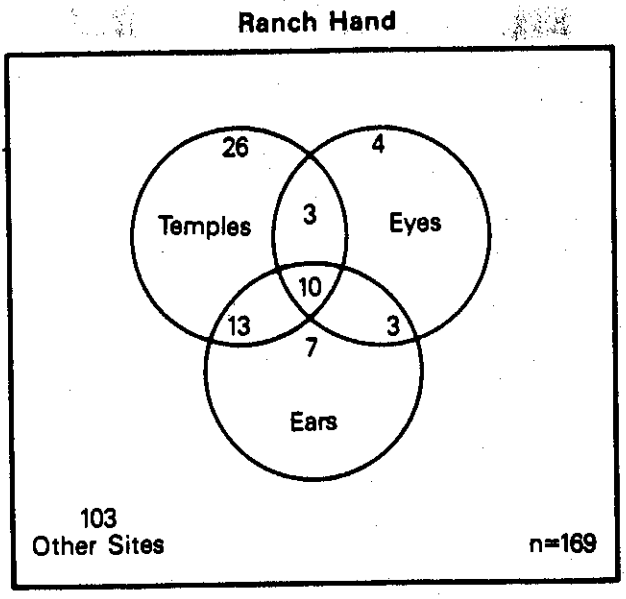
The Ranch Hand and Comparison Venn diagrams were contrasted by chi-square analysis of a 2x8 table, and no difference in the spatial distribution was noted for the combination of pre- and post-SEA and post-SEA groups ($p=0.706$), or for the analysis of only the post-SEA group ($p=0.699$). Sparse data cells were present in the analysis of both figures. Differences in spatial distributions were also not evident when the "other sites" classification was deleted ($p=0.770$ and $p=0.664$, respectively). If the intersection of the circles in these figures (i.e., temples, ears, and eyes) is contrasted with the rest of the locations of acne, no significant difference is seen ($p=0.189$ and $p=0.627$ for the combination of post-SEA and pre- and post-SEA groups and for only the post-SEA group, respectively).

Physical Examination Data

Twenty-two skin disorders were assessed at the dermatological examination (page C-9 of Appendix C). These disorders were combined into eight variables for analytic purposes. Comedones, acneiform lesions, acneiform scars, depigmentation, inclusion cysts, and hyperpigmentation were analyzed separately. The remaining 16 conditions were grouped to form a broad variable called "other abnormalities." Analysis of skin cancer is included in the malignancy chapter and will not be discussed here. Additionally, comedones, acneiform lesions, acneiform scars, and inclusion cysts were grouped to construct a dermatology index, which summed the number of abnormalities for these four conditions for each participant. Logistic regression techniques, with the use of BMDP®-LR, were utilized for adjusted analysis of all these variables except the dermatology index, which used BMDP®-4F. The sample sizes were sufficient to detect a 27-percent increase in the prevalence rate for comedones, a 30 percent increase in the prevalence rate for acneiform scars, and a 12 percent increase in the prevalence of at least one abnormality for the dermatology index, using a two-sided α-level of 0.05 with a power of 0.80. No cases of chloracne were chemically diagnosed.

Preliminary Dependent Variables and Covariate Relationships

The association of the eight skin disorder variables in both groups and the covariates of age (born in or after 1942, born between 1923 and 1941, born in or before 1922), race (Black or nonblack), occupation, and presence of pre-SEA acne (yes/no) was assessed using Pearson's Chi-square test and Fisher's exact test. Table 14-5 is a summary of the associations of the dependent variables with these four covariates. Seven additional participants, who were initially classified as "undetermined," were reclassified as having acne before duty in SEA, based on data gathered by telephone. Nineteen participants were omitted from analyses involving presence of pre-SEA acne, because historical information on the date of onset of acne was not available.



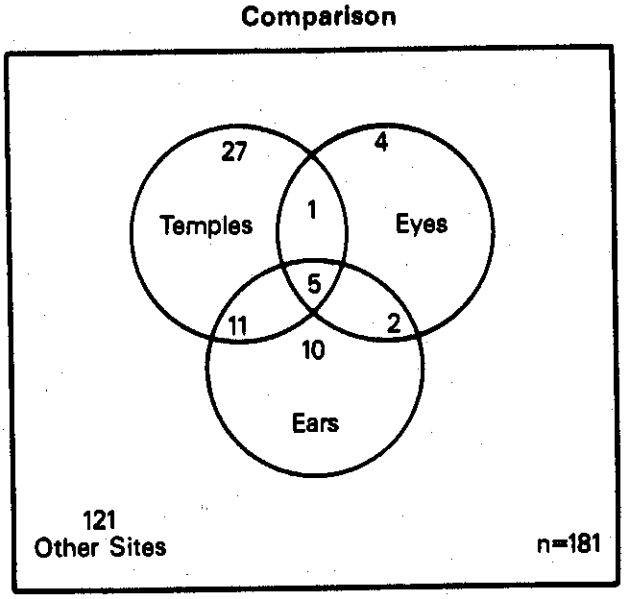
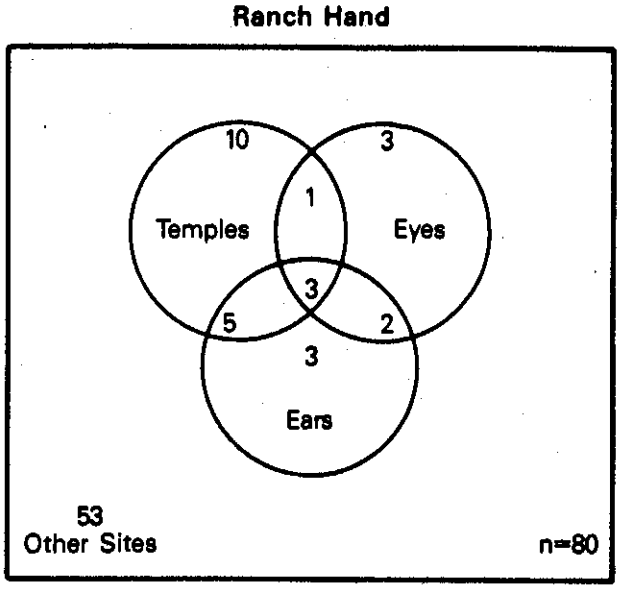


Figure 14-2.
Location of Post-SEA and Pre- and Post-SEA Acne by Group



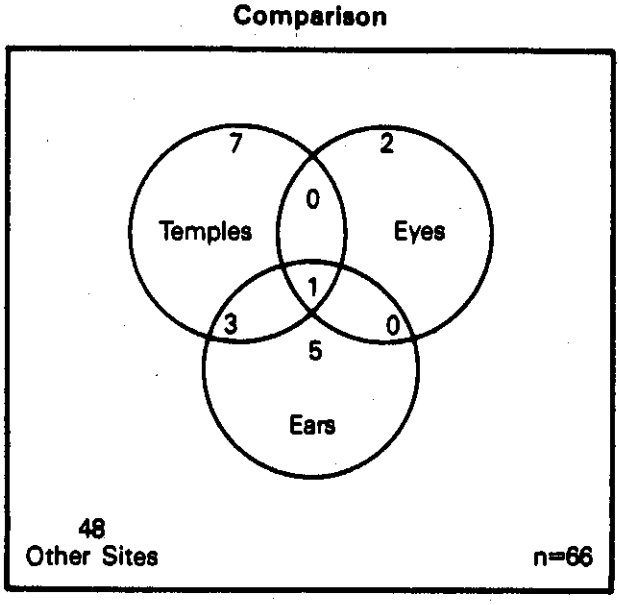


Figure 14-3.
Location of Post-SEA and Acne by Group

TABLE 14-5.

Association Between Dermatological Variables and Age, Race, Occupation, and Pre-SEA Acne in the Combined Ranch Hand and Comparison Groups

Variable	Age	Race	Occupation	Pre-SEA Acne
Comedones	<0.001	<0.001	<0.001	NS
Acneiform Lesions	<0.001	NS*	NS*	<0.001
Acneiform Scars	<0.001	<0.001	<0.001	<0.001
Depigmentation	NS	0.009	NS	NS
Inclusion Cysts	NS	NS	0.036	NS
Hyperpigmentation	NS	<0.001	<0.001	0.003
Other Abnormalities	<0.001	<0.001	<0.001	NS*
Dermatology Index	NS	NS	0.010	<0.001

NS: Not significant ($p>0.10$)

NS*: Borderline significant ($0.05<p\leq0.10$) effect with variable.

Age had a significant effect on four of the variables. Prevalence rates for comedones and other abnormalities were highest for older participants (born in or before 1922). On the other hand, the prevalence of acneiform lesions and acneiform scars was higher in the younger participants (born in or after 1942).

Nonblacks had a significantly higher prevalence of comedones and other abnormalities and a marginally significant increase ($p=0.055$) in acneiform lesions. Blacks had a significantly higher prevalence rate for acneiform scars, depigmentation, and hyperpigmentation.

Occupation had a significant or marginally significant effect on seven of the eight variables, with either enlisted flyers or enlisted groundcrew generally having a higher percentage of abnormalities.

Participants with pre-SEA acne had a significantly higher prevalence rate for acneiform lesions and acneiform scars, and a higher percentage with at least one abnormality in the dermatology index. Participants without acne pre-SEA had a significantly higher prevalence rate for hyperpigmentation, and a marginally significantly higher prevalence rate ($p=0.084$) for other abnormalities.

Analyses of Individual Dependent Variables

Comedones

As reflected in Table 14-6, there was not a significant difference ($p=0.361$) between the proportion of participants with comedones in the Ranch Hand and Comparison groups, unadjusted for any covariates.

TABLE 14-6.

Unadjusted Analysis for Comedones by Group

Group	Comedones: Present Number	Comedones: Present Percent	Comedones: Absent Number	Comedones: Absent Percent	Total	Summary Statistics
Ranch Hand	250	24.6	766	75.4	1,016	Est. RR: 0.91
Comparison	340	26.3	952	73.7	1,292	95% C.I.: (0.76,1.10)
						p-Value: 0.361

Tests of association between the presence of comedones in both groups and the four covariates indicated that there was not a significant effect due to the presence of pre-SEA acne ($p=0.355$), but that there were significant effects due to occupation ($p<0.001$), age ($p<0.001$), and race ($p<0.001$). The proportion of participants with comedones increased with age (18.9% for participants born in or after 1942, 29.8% for participants born between 1923 and 1941, and 37.9% for participants born in or before 1922). Significantly more nonblacks had comedones than Blacks (26.5% versus 11.9%), and enlisted flyers had more than enlisted groundcrew or officers (34.4%, 24.8%, and 22.6%, respectively).

An adjusted analysis of the proportion of participants with comedones was performed using logistic regression techniques. Results are presented in Table 14-7.

TABLE 14-7.

Adjusted Analysis for Comedones by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,007	1,282	0.89 (0.74,1.09)	0.260	Occupation ($p<0.001$) Presence of Pre-SEA Acne ($p=0.038$) Race-by-Age ($p=0.046$)

Again, no significant differences were found between groups (p=0.260). Occupation, pre-SEA acne, and a race-by-age interaction were significant (p<0.001, p=0.038, and p=0.046, respectively).

Compared to Baseline findings, the percentage of participants with comedones increased in the Comparison group but decreased in the Ranch Hand group. Estimated and adjusted relative risks were both less than 1.0 in the followup study, while the estimated relative risk in the Baseline study was slightly greater than 1.0 (RR=1.05, with Original Comparisons used), but statistically nonsignificant.

Acneiform Lesions

As shown in Table 14-8, there was not a significant difference between the proportion of participants with acneiform lesions in the Ranch Hand and Comparison groups, unadjusted for any covariates (p=0.624).

TABLE 14-8.

Unadjusted Analysis for Acneiform Lesions by Group

	Acneiform Lesions					
	Present		Absent			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	188	18.5	828	81.5	1,016	Est. RR: 1.06
Comparison	228	17.6	1,064	82.4	1,292	95% C.I.: (0.86,1.31)
						p-Value: 0.624

Tests of association between the presence of acneiform lesions in both groups and the four covariates revealed marginally significant effects due to race (p=0.055) and occupation (p=0.064), and significant effects for age (p<0.001) and presence of pre-SEA acne (p<0.001). Nonblacks had a marginally significantly higher proportion of participants with acneiform lesions than Blacks (18.4% versus 11.9%). The proportion of participants with lesions was greatest for enlisted groundcrew (20.1%), as compared to the other occupations (officers, 16.4%; enlisted flyers, 16.0%). The proportion of participants with acneiform lesions decreased with age (born in or after 1942, 23.0%; born between 1923 and 1941, 14.8%; born in or before 1922, 10.3%). A significantly higher proportion of participants with acne present before SEA had lesions (22.4%), as compared with those not having acne before SEA (16.0%).

An adjusted analysis of the proportion of participants with acneiform lesions was performed using logistic regression techniques. Results of this analysis are summarized in Table 14-9.

TABLE 14-9.

Adjusted Analysis for Acneiform Lesions by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,007	1,282	1.08 (0.87,1.34)	0.512	Age (p<0.001) Race (p=0.014) Presence of Pre-SEA Acne (p=0.008)

The results showed no significant differences between groups (p=0.512). Age (p<0.001), race (p=0.014), and presence of pre-SEA acne (p=0.008) were significant adjusting variables in this analysis. The Baseline and followup results for acneiform lesions were nearly identical with respect to group differences.

Acneiform Scars

Table 14-10 shows no significant difference between the proportion of participants with acneiform scars in the Ranch Hand and Comparison groups, unadjusted for any covariates (p=0.720).

TABLE 14-10.

Unadjusted Analysis for Acneiform Scars by Group

	Acneiform Scars					
	Present		Absent			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	150	14.8	866	85.2	1,016	Est. RR: 1.05
Comparison	183	14.2	1,109	85.8	1,292	95% C.I.: (0.83,1.33)
						p-Value: 0.720

Tests of association between the presence of acneiform scars in both groups and the covariates disclosed significant effects due to the four variables (p<0.001). As age increased, the proportion of participants with

acneiform scars decreased (17.9% for participants born in or after 1942, 12.4% for participants born between 1923 and 1941, and 5.7% for participants born in or before 1922). Significantly more Blacks had scars than nonblacks (28.0% and 13.5%, respectively), and enlisted personnel had more than officers (enlisted groundcrew, 16.9%; enlisted flyers, 16.5%; and officers, 10.4%). The pre-SEA acne classification had a significantly higher proportion of participants with acneiform scars than the non pre-SEA acne classification.

An adjusted analysis of the proportion of participants with acneiform scars was performed using logistic regression techniques. Results are given in Table 14-11.

TABLE 14-11.

Adjusted Analysis for Acneiform Scars by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,007	1,282	1.07 (0.84,1.36)	0.584	Age (p=0.006) Race (p<0.001) Occupation (p=0.016) Presence of Pre-SEA Acne (p<0.001)

No significant group differences were found (p=0.584). As in the covariate analysis with acneiform scars, significant effects in the adjusted analysis were observed due to all four covariates (age, p=0.006; race, p<0.001; occupation, p=0.016; presence of pre-SEA acne, p<0.001). The results for acneiform scars, as with the acneiform lesions, were quite similar in the followup and Baseline studies.

Depigmentation

Table 14-12 shows the contrast between the proportion of participants with depigmentation in the Ranch Hand and Comparison groups, unadjusted for any covariates. The proportion of participants with depigmentation was greater in the Comparison than in the Ranch Hand group; however, the difference between groups was nonsignificant (p=0.143).

TABLE 14-12.

Unadjusted Analysis for Depigmentation by Group

Group	Depigmentation: Present Number	Depigmentation: Present Percent	Depigmentation: Absent Number	Depigmentation: Absent Percent	Total	Summary Statistics
Ranch Hand	102	10.0	914	90.0	1,016	Est. RR: 0.82
Comparison	155	12.0	1,137	88.0	1,292	95% C.I.: (0.63,1.07) p-Value: 0.143

Tests of association between the presence of depigmentation in both groups and the four covariates determined a significant effect due to race (p=0.009), but showed nonsignificant effects for age, occupation, and presence of pre-SEA acne.

An adjusted analysis of the proportion of participants with depigmentation was performed using logistic regression techniques. The statistics are presented in Table 14-13.

TABLE 14-13.

Adjusted Analysis for Depigmentation by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,016	1,292	0.82 (0.63,1.07)	0.144	Race (p=0.010)

No significant difference was observed between groups (p=0.144). Race was the only significant covariate in this adjusted analysis (p=0.010). Depigmentation was not analyzed in the Baseline study.

Inclusion Cysts

As reflected in Table 14-14, there was not a significant difference between the proportion of participants with inclusion cysts in the Ranch Hand and Comparison groups, unadjusted for any covariates (p=0.303).

TABLE 14-14.

Unadjusted Analysis for Inclusion Cysts by Group

Group	Inclusion Cysts: Present Number	Present Percent	Absent Number	Absent Percent	Total	Summary Statistics
Ranch Hand	114	11.2	902	88.8	1,016	Est. RR: 0.87
Comparison	164	12.7	1,128	87.3	1,292	95% C.I.: (0.67,1.12)
						p-Value: 0.303

Tests of association between the presence of inclusion cysts in both groups and the covariates of age, race, occupation, and presence of pre-SEA acne showed no significant effects due to age (p=0.437), race (p=0.506), or presence of pre-SEA acne (p=0.449). Occupation, however, exhibited a significant effect (p=0.036), with the enlisted flyer category having the highest proportion of participants with inclusion cysts (15.8% versus 11.9% and 10.8% for officers and enlisted groundcrew, respectively.

An adjusted analysis of the proportion of participants with inclusion cysts was performed using logistic regression techniques. Results are presented in Table 14-15.

TABLE 14-15.

Adjusted Analysis for Inclusion Cysts by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,016	1,292	0.86 (0.67,1.12)	0.260	Occupation (p=0.041)

No significant differences for inclusion cysts were found between the Ranch Hand and the Comparison groups (p=0.260). Occupation was the only significant covariate in this analysis (p=0.041).

With reference to the Baseline study, the percentage of participants with inclusion cysts at the followup increased in the Comparison group, and

decreased slightly in the Ranch Hand group. These differences could be due to changes in disease over time, different examiners, or changes in the cohorts examined. Both estimated and adjusted relative risks were less than one in the followup, while the estimated relative risk at the Baseline was slightly greater than one (RR=1.10 for Original Comparisons) but was not statistically significant.

Hyperpigmentation

Table 14-16 shows there was not a significant difference between the proportion of participants with hyperpigmentation in the Ranch Hand and Comparison groups, unadjusted for any covariates (p=0.762).

TABLE 14-16.

Unadjusted Analysis for Hyperpigmentation by Group

	Hyperpigmentation					
	Present		Absent			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	228	22.4	788	77.6	1,016	Est. RR: 1.03
Comparison	283	21.9	1,009	78.1	1,292	95% C.I.: (0.85,1.26)
						p-Value: 0.762

Tests of association between the presence of hyperpigmentation in both groups and the four covariates revealed there was not a significant effect due to age (p=0.833), but that significant effects were due to race (p<0.001), occupation (p<0.001), and presence of pre-SEA acne (p=0.003). Blacks had a much higher prevalence of hyperpigmentation than nonblacks (53.1% for Blacks, 20.1% for nonblacks), and enlisted personnel had a higher prevalence of hyperpigmentation than officers (enlisted groundcrew, 25.5%; enlisted flyers, 23.5%; officers, 17.4%). The proportion of participants with hyperpigmentation was greater in the absence of pre-SEA acne (23.8%) than in the presence of pre-SEA acne (18.2%).

An adjusted analysis of the proportion of participants with hyperpigmentation was performed using logistic regression techniques. Results are given in Table 14-17.

TABLE 14-17.

Adjusted Analysis for Hyperpigmentation by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,007	1,282	1.04 (0.85,1.27)	0.720	Race ($p<0.001$) Occupation ($p=0.009$) Presence of Pre-SEA Acne ($p=0.009$)

No significant group differences ($p=0.720$) were noted, although significant effects of race ($p<0.001$), occupation ($p=0.009$), and presence of pre-SEA acne ($p=0.009$) were evident.

The proportion of participants with hyperpigmentation has increased since the Baseline study. Almost three times as many abnormalities were found at the followup study (approximately 22% versus 8%). The relative risk estimate was closer to 1 in the followup study, but relative risks from both the Baseline and followup studies were not significantly different from 1. These differences could be due to disease or examination techniques.

Other Abnormalities

The study of other abnormalities encompassed a wide range of dermatological disorders. Included in this variable were the following abnormalities:

(1) Jaundice
(2) Spider Angiomata
(3) Palmar Erythema
(4) Suspected Melanoma
(5) Palmar Keratoses
(6) Actinic Keratoses
(7) Petechiae
(8) Ecchymoses
(9) Conjunctival Abnormality
(10) Oral Mucosal Abnormality
(11) Fingernail Abnormality
(12) Toenail Abnormality
(13) Dermatographia
(14) Cutis Rhomboidalis
(15) Suspected Basal Cell Carcinoma
(16) Suspected Squamous Cell Carcinoma

With respect to the category "Other Abnormalities," a participant was considered normal only if he was negative for all of these conditions. If one or more abnormalities existed, then the participant was considered abnormal.

As reflected in Table 14-18, there was not a significant difference between the proportion of participants with other abnormalities in the Ranch Hand and Comparison groups, unadjusted for any covariates (p=0.349).

TABLE 14-18.

Unadjusted Analysis for Other Abnormalities by Group

	Other Abnormalities					
	Abnormal		Normal			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	608	59.8	408	40.2	1,016	Est. RR: 1.08 95% C.I.: (0.92,1.28) p-Value: 0.349
Comparison	748	57.9	544	42.1	1,292	

Tests of association between the presence of other abnormalities in both groups and the four covariates found a marginally significant effect due to the presence of pre-SEA acne (p=0.084), and significant effects due to age (p<0.001), occupation (p<0.001), and race (p<0.001). The proportion of participants with other abnormalities in the absence of pre-SEA acne (59.9%) was marginally significantly larger than the proportion of participants with other abnormalities who also had pre-SEA acne (56.1%). The proportion of participants with other abnormalities increased with age (with a low of 43.3% for participants born in or after 1942 to a high of 82.8% for participants born in or before 1922). Nonblacks had a significantly and substantially higher percentage of other abnormalities than Blacks (60.3% and 35.7%, respectively). Enlisted groundcrew had a lower proportion of abnormalities than officers or enlisted flyers (53.3%, 63.2%, and 63.8%, respectively).

An adjusted analysis of the proportion of participants with other abnormalities was performed using logistic regression techniques. Results are presented in Table 14-19.

Again, no significant difference was observed between groups (p=0.432). Age and race were significant covariates in this analysis (p<0.001 for both).

In reference to the Baseline study, the percentage of participants with other abnormalities has increased in both the Comparison and the Ranch Hand groups. In the Baseline study, the estimated relative risk for Ranch Hands versus Original Comparisons was 0.77, significantly less than 1.00. The estimate of the relative risk has increased in the followup study to 1.08. The percentage of other abnormalities has increased from approximately 14 percent in the Baseline study to nearly 59 percent in the followup study.

TABLE 14-19.

Adjusted Analysis for Other Abnormalities by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,016	1,292	1.07 (0.90,1.28)	0.432	Age (p<0.001) Race (p<0.001)

Dermatology Index

Four of the previously analyzed conditions (comedones, acneiform lesions, acneiform scars, and inclusion cysts) were used to construct a dermatology index. All four conditions are indicators of possible chloracne. The index was formulated by counting the number of abnormalities present in a participant for the four conditions. Consequently, the dermatology index ranged from 0 to 4, where 0 indicated that the participant had none of these abnormalities and 4 indicated that the participant had all of these abnormalities.

Table 14-20 presents the number and the percent of participants with each of these five scores by group. A significant difference between the Ranch Hand and Comparison groups was not observed for this dermatology index, unadjusted for any covariates (p=0.576, 4 d.f.).

Covariate main effect analyses found nonsignificant effects due to age (p=0.407) and race (p=0.558), but significant effects for occupation (p=0.010) and the presence of acne pre-SEA (p<0.001). These data are summarized in Table 14-21. By occupation, 55.8 percent of the officers had no abnormalities, whereas 50.8 percent of the enlisted groundcrew and 44.4 percent of the enlisted flyers had no abnormalities. The stratum corresponding to participants with pre-SEA acne present had a larger percentage of participants with at least one abnormality (see Table 14-21).

An adjusted analysis of the five scores of the dermatology index was performed using log-linear modeling techniques. Significant effects were noted for occupation and an interaction between group and presence of pre-SEA acne (p=0.005, p=0.041, respectively). Consequently, an analysis, stratifying by pre-SEA acne status, was performed, and the results are shown in Table 14-22.

The adjusted relative risk for each of the index scores (1 to 4, separately, versus the 0 score), the 95 percent confidence interval, and the p-value for each contrast for each pre-SEA acne class are given in Table 14-23.

TABLE 14-20.

Unadjusted Analysis for the Dermatology Index by Group

	Dermatology Index Score										
	0		1		2		3		4		
Group	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Total
Ranch Hand	533	52.5	318	31.3	121	11.9	34	3.3	10	1.0	1,016
Comparison	658	50.9	420	32.5	154	11.9	53	4.1	7	0.5	1,292

Overall p-Value (4 d.f.)=0.576

Contrast	Est. Relative Risk (95% C.I.)	p-Value*
1 vs. 0	0.94 (0.78,1.13)	0.480
2 vs. 0	0.97 (0.75,1.26)	0.840
3 vs. 0	0.79 (0.51,1.24)	0.317
4 vs. 0	1.76 (0.67,4.66)	0.327

*Fisher's exact test.

TABLE 14-21.

Association Between the Dermatology Index and Age, Race, Occupation, and Presence of Pre-SEA Acne in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Dermatology Index Score* 0 Number	0 Percent	1 Number	1 Percent	2 Number	2 Percent	3 Number	3 Percent	4 Number	4 Percent	Total[a]	p-Value[b]
Age	Born ≥1942	501	52.2	296	30.8	114	11.9	40	4.2	9	0.9	960	0.407
	Born 1923-1941	647	51.3	408	32.4	156	12.4	42	3.3	8	0.6	1,261	
	Born ≤1922	43	49.4	34	39.1	5	5.7	5	5.7	0	0.0	87	
Race	Black	83	58.0	38	26.6	17	11.9	4	2.8	1	0.7	143	0.558
	Nonblack	1,108	51.2	700	32.3	258	11.9	83	3.8	16	0.8	2165	
Occupation													
	Officer	482	55.8	265	30.7	91	10.5	21	2.4	5	0.6	864	0.010
	Enlisted Flyer	172	44.4	135	34.9	58	15.0	19	4.9	3	0.8	387	
	Enlisted Groundcrew	537	50.8	338	32.0	126	11.9	47	4.4	9	0.9	1,057	
Presence of Pre-Sea Acne**	No	842	54.0	514	32.9	153	9.8	44	2.8	7	0.4	1,560	<0.001
	Yes	337	46.2	220	30.1	121	16.6	42	5.8	9	1.2	729	

* Score denotes the number of abnormalities (for comedones, acneiform lesions, acneiform scars, and inclusion cysts) diagnosed.

**Nineteen participants could not be classified.

[a] One participant refused to take the dermatology examination.

[b] Pearson's chi-square test.

TABLE 14-22.

Adjusted Analysis for the Dermatology Index by SEA Acne Class and Group

Pre-SEA Acne Class	Group	Dermatology Index Score*										
		0		1		2		3		4		
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Total
No pre-SEA acne	Ranch Hand	360	52.6	234	34.2	69	10.1	16	2.3	5	0.7	684
	Comparison	482	55.0	280	32.0	84	9.6	28	3.2	2	0.2	876
Pre-SEA acne	Ranch Hand	167	51.7	82	25.4	51	15.8	18	5.6	5	1.5	323
	Comparison	170	41.9	138	34.0	70	17.2	24	5.9	4	1.0	406

*Score denotes the number of abnormalities (comedones, acneiform lesions, acneiform scars, and inclusion cysts) diagnosed.

TABLE 14-23.

Adjusted Relative Risks for Contrasts of Dermatology Index by Pre-SEA Class

Pre-SEA Acne	Contrast	Adjusted Relative Risk	95% C.I.	p-Value
No	1 abnormality vs. 0 abnormalities	1.12	(0.90,1.39)	0.315
	2 vs. 0	1.10	(0.77,1.55)	0.605
	3 vs. 0	0.77	(0.41,1.44)	0.411
	4 vs. 0	3.09	(0.65,14.62)	0.155
Yes	1 vs. 0	0.60	(0.42,0.85)	0.004
	2 vs. 0	0.73	(0.48,1.12)	0.148
	3 vs. 0	0.75	(0.39,1.43)	0.380
	4 vs. 0	1.19	(0.33,4.38)	0.788

This analysis showed a significant difference between groups only when contrasting the proportion of participants with one abnormality (out of four) to the proportion of participants with no abnormalities for participants with pre-SEA acne ($p=0.004$). However, Comparisons were more likely to have one abnormality than the Ranch Hands, as is evidenced by the relative risk and confidence interval being less than 1.

In contrast to the Baseline study, the percentage of participants with a score of 1 or more has increased at the followup examination for both the Ranch Hand and Comparison groups (8.1% for Ranch Hands, 12.1% for Comparisons). The estimated relative risks, when the dermatology index is condensed into two categories, were 1.11 for the Baseline examination and 0.94 for the followup examination.

Biopsy Results

Dermatologists were instructed to perform skin biopsies on any lesions they suspected of being malignant. Of the 40 biopsies collected from 35 participants, none was suggestive of chloracne. Histologic descriptions of these biopsies are presented in Table 14-24. With the exception of confirmed basal cell carcinoma, no single diagnostic category predominated.

TABLE 14-24.

Summary of Histologic Descriptions
of Skin Biopsy by Group

Histologic Description	Group		Comments
	Ranch Hand	Comparison	
Basal Cell Carcinoma	7	4	a,b
Suspected Basal Cell Carcinoma	0	3	b
Suspected Unspecified Carcinoma	0	1	
Unspecified Carcinoma	1	0	c
Dermatofibroma	3	0	
Pigmented Nevus	1	2	
Dyschromia	1	0	d
Keratoderma, Acquired	1	1	a
Melanoacanthoma (Papilloma)	0	1	
Intradermal Nevus	1	0	
Junctional Nevus	0	1	
Cavernous Hemangioma	0	1	
Degenerative Skin Disorder	0	1	
Other Specified Disorders of Skin	0	1	
Local Infection of Skin	1	0	c
Other Dermatoses	5	2	c
Total	21	18	

[a]One participant had a basal cell carcinoma at one site and an acquired keratoderma at another site.

[b]One participant had a basal cell carcinoma at one site and a suspected basal cell carcinoma at another site.

[c]One participant had a local infection of the skin, a suspected unspecified carcinoma, and a dermatosis at the same site.

[d]One participant had two cases of dyschromia at two different sites.

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted within each occupational cohort of the Ranch Hand group to search for dose-response relationships (see Chapter 8 for details on the exposure index). The dermatology index was collapsed into two categories, 0 and greater than 0. All eight dermatological variables were explored, unadjusted for any covariates, using Pearson's chi-square test and Fisher's exact test. Adjusted analyses were performed by logistic regression for these variables, using age, race, presence of pre-SEA acne, and any significant pairwise interactions between the exposure index and these covariates. Overall significance in the proportion of abnormalities among the exposure index levels of low, medium, and high was determined, as well as contrasts in the proportion of abnormalities between the medium and low exposure levels, and between the high and low exposure levels. Age was used as a continuous variable in the adjusted analyses.

Results of the adjusted analyses for these eight variables are presented in Table 14-25, and counterpart results for unadjusted analyses are presented in Table L-1 of Appendix L. Results from further investigation of exposure index by covariate interactions are given in Table L-2 of Appendix L.

Significant or marginally significant results were present for some of these variables based on unadjusted analyses. A borderline significantly higher prevalence of comedones (Est. RR: 1.78, 95% C.I.: [0.95,3.35], p=0.084) for the contrast of medium exposure to low exposure was seen for officers. Marginally significant results for the contrast of high exposure to low exposure were also present for acneiform scars for officers (Est. RR: 2.38, 95% C.I.: [0.94,6.06], p=0.075) and enlisted groundcrew (Est. RR: 1.82, 95% C.I.: [1.00,3.30], p=0.053), as well as for other abnormalities for officers (Est. RR: 1.66, 95% C.I.: [0.98,2.78], p=0.067). The data for these last three variable-occupation combinations supported an increase in the proportion of abnormalities from low to high exposure. Significant or marginally significant results were also observed for medium exposure versus low exposure in officers and enlisted groundcrew for depigmentation, and for high exposure versus low exposure in other abnormalities with enlisted flyers, but prevalence decreased as the exposure level increased in these cases.

The frequency of abnormalities for the different exposure index levels exhibited no consistent pattern across occupations. However, within the officer and enlisted groundcrew occupations, most variables showed the low exposure level to have the lowest prevalence of abnormalities or the high exposure level to have the highest prevalence, whereas very few variables showed this pattern for enlisted flyers.

Adjusted analyses revealed patterns similar to those of the unadjusted analyses. Results of the counterpart adjusted analyses to the situations described above are detailed below.

(1) Comedones in officers, medium versus low: Adj. RR: 1.62, 95% C.I.: (0.83,3.15), p=0.154.

TABLE 14-25.

Adjusted Exposure Index Analysis for Dermatological 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
Comedones	Officer	126	129	122	Overall		0.334
					M vs. L	1.62 (0.83,3.15)	0.154
					H vs. L	1.44 (0.74,2.83)	0.283
	Enlisted Flyer	55	65	56	Overall		0.413
					M vs. L	0.65 (0.30,1.41)	0.276
					H vs. L	0.61 (0.27,1.37)	0.234
	Enlisted Groundcrew	152	162	140	Overall		0.878
					M vs. L	0.94 (0.55,1.60)	0.808
					H vs. L	1.08 (0.63,1.83)	0.782
Acneiform Lesions	Officer	126	129	122	Overall		0.669
					M vs. L	1.06 (0.52,2.15)	0.880
					H vs. L	1.34 (0.67,2.66)	0.409
	Enlisted Flyer	55	65	56	Overall		0.917
					M vs. L	0.91 (0.32,2.60)	0.856
					H vs. L	1.14 (0.39,3.35)	0.814
	Enlisted Groundcrew	152	162	140	Overall		0.674
					M vs. L	1.01 (0.58,1.75)	0.973
					H vs. L	1.25 (0.71,2.20)	0.431

TABLE 14-25. (continued)

Adjusted Exposure Index Analysis for Dermatological 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	126	129	122	Overall		****(1)
					M vs. L	****(1)	****(1)
					H vs. L	****(1)	****(1)
Acneiform Scars	Enlisted Flyer	55	65	56	Overall		0.363
					M vs. L	0.82 (0.31,2.13)	0.682
					H vs. L	0.47 (0.16,1.39)	0.174
	Enlisted Groundcrew[a]	152	162	140	Overall		0.068
					M vs. L	1.22 (0.66,2.27)	0.519
					H vs. L	2.00 (1.08,3.67)	0.026
	Officer	126	129	122	Overall		0.006
					M vs. L	0.33 (0.11,0.98)	0.045
					H vs. L	1.50 (0.69,3.25)	0.302
Depigmentation	Enlisted Flyer	55	65	56	Overall		0.493
					M vs. L	0.53 (0.18,1.54)	0.245
					H vs. L	0.67 (0.24,1.90)	0.450
	Enlisted Groundcrew	152	162	140	Overall		****(2)
					M vs. L	****(2)	****(2)
					H vs. L	****(2)	****(2)

TABLE 14-25. (continued)

Adjusted Exposure Index Analysis for Dermatological 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[b]	126	129	122	Overall		0.221
					M vs. L	2.05 (0.91,4.60)	0.082
					H vs. L	1.32 (0.56,3.11)	0.532
Inclusion Cysts	Enlisted Flyer	55	65	56	Overall		0.881
					M vs. L	1.24 (0.41,3.78)	0.707
					H vs. L	1.33 (0.42,4.17)	0.630
	Enlisted Groundcrew	152	162	140	Overall		0.916
					M vs. L	0.91 (0.43,1.93)	0.806
					H vs. L	1.07 (0.51,2.24)	0.856
	Officer	126	129	122	Overall		0.813
					M vs. L	0.92 (0.47,1.79)	0.807
					H vs. L	0.80 (0.41,1.58)	0.525
Hyperpig-mentation	Enlisted Flyer	55	65	56	Overall		0.656
					M vs. L	0.71 (0.29,1.76)	0.465
					H vs. L	1.04 (0.43,2.53)	0.930
	Enlisted Groundcrew	152	162	140	Overall		0.365
					M vs. L	1.20 (0.71,2.01)	0.494
					H vs. L	0.81 (0.46,1.41)	0.450

TABLE 14-25. (continued)

Adjusted Exposure Index Analysis for Dermatological 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
Other Abnormalities	Officer	126	129	122	Overall		0.309
					M vs. L	1.30 (0.75,2.24)	0.346
					H vs. L	1.53 (0.88,2.65)	0.129
	Enlisted Flyer	55	65	56	Overall		0.049
					M vs. L	0.66 (0.28,1.56)	0.341
					H vs. L	0.35 (0.14,0.83)	0.018
	Enlisted Groundcrew	152	162	140	Overall		0.764
					M vs. L	0.85 (0.52,1.36)	0.489
					H vs. L	0.87 (0.52,1.43)	0.580
Dermatology Index	Officer	126	129	122	Overall		****(1)
					M vs. L	****(1)	****(1)
					H vs. L	****(1)	****(1)
	Enlisted Flyer	55	65	56	Overall		0.618
					M vs. L	0.74 (0.36,1.54)	0.423
					H vs. L	0.71 (0.33,1.51)	0.368
	Enlisted Groundcrew	152	162	140	Overall		0.469
					M vs. L	1.01 (0.65,1.59)	0.955
					H vs. L	1.30 (0.82,2.06)	0.270

[a]Marginal exposure index-by-presence of pre-SEA acne interaction (p=0.056)--relative risk, confidence interval and p-value presented, and additional information provided in interaction summaries.

****(1): Exposure index-by-presence of pre-SEA acne and exposure index-by-race interaction--relative risk, confidence interval, and p-value not presented.

****(2): Exposure index-by-presence of pre-SEA acne interaction--relative risk, confidence interval and p-value not presented.

(2) Acneiform scars in officers, high versus low: interaction present; direct contrast of adjusted and unadjusted analyses not possible.

(3) Acneiform scars in enlisted groundcrew, high versus low: Adj. RR: 2.00, 95% C.I.: (1.08,3.67), p=0.026; overall p-value=0.068, increase in the proportion of abnormalities with increasing exposure levels supported.

(4) Other abnormalities in officers, high versus low: Adj. RR: 1.53, 95% C.I.: (0.88,2.65), p=0.129.

Other adjusted analyses that showed significance or marginal significance exhibited a decreasing prevalence with increasing exposure level. All other adjusted analyses showed an interaction with covariates (described below) or nonsignificant results.

Interactions were present for three of the eight variables and were observed for officers and enlisted groundcrew. A summary of these interactions is presented below in Table 14-26.

TABLE 14-26.

Summary of Exposure Index by Covariate Interactions Encountered in Adjusted Analysis of Dermatological Variables

Variable	Occupation	Covariate	p-Value
Acneiform Scars	Officer	Race	0.003
Acneiform Scars	Officer	Presence of Pre-SEA acne	0.003
Acneiform Scars	Enlisted Groundcrew	Presence of Pre-SEA acne	(marginal) 0.056
Depigmentation	Enlisted Groundcrew	Presence of Pre-SEA acne	0.035
Dermatology Index*	Officer	Race	0.026
Dermatology Index*	Officer	Presence of Pre-SEA acne	0.029

*Variable was collapsed into two categories, 0 and >0.

As can be seen, all variables and occupations with interactions had a significant exposure index-by-presence of pre-SEA acne interaction or significant exposure index-by-race and exposure index-by-presence of pre-SEA acne interactions. Meaningful interpretation of many of the subsequent stratified analyses was hindered by small sample sizes, but two situations were of particular interest. For acneiform scars on officers, nonblack personnel without pre-SEA acne at low exposure had no participants with scars, whereas nonblack personnel exposed at the medium and high levels had 7.8 percent and 10.5 percent of participants with scars, respectively. Also, with acneiform scars for enlisted groundcrew, an increase in the prevalence of abnormalities for increasing levels of exposure was present for participants with pre-SEA acne, with an adjusted relative risk of 5.38 (95% C.I.: [1.45,19.96], p=0.012) for the contrast of high exposure versus low exposure.

In summary, the results suggested the presence of an increasing dose-response relationship in certain occupations for a few of the dermatological variables or within substrata of these variables, but no consistent pattern was evident throughout the dermatological exposure index evaluation.

LONGITUDINAL ANALYSES

The dermatology index was chosen to assess longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. In testing for this difference, the dermatology index scores were collapsed into two categories: normal (dermatology index score of 0) and abnormal (dermatology index score greater than 0). As shown in Table 14-27, 2x2 tables were constructed for each group. These tables show the number of participants who were abnormal at the Baseline examination and abnormal at the followup, abnormal at Baseline and normal at followup, normal at Baseline and abnormal at followup, and normal at both Baseline and followup. The odds ratios given are the ratios 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).

TABLE 14-27.

Longitudinal Analysis of the Dermatology Index: A Contrast of Baseline and First Followup Examination Abnormalities

Group	1982 Baseline Exam	1985 Followup Exam: Abnormal	1985 Followup Exam: Normal	Odds Ratio (OR)*	p-Value (OR_{RH} vs OR_C)
Ranch Hand	Abnormal	241	136	1.68	
	Normal	228	366		
Comparison	Abnormal	283	136	2.08	0.15
	Normal	283	437		

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

The changes in normal/abnormal status within each group were compared, and the p-value given was derived from Pearson's chi-square test of the hypothesis that the pattern of change in the two groups was the same. These results showed that the difference in the pattern is not significant (p=0.15).

DISCUSSION

The relative risks for all eight dermatological variables approached unity (none was statistically significant), an observation previously noted at the Baseline examination (except for the category "Other Abnormalities," which predominated in the Comparisons). More dermatological abnormalities were recorded at the followup (for six of the seven variables shared between the examinations) than at the Baseline--the increase in detection was slightly stronger in the Comparison group than in the Ranch Hand group. For example, in the category "Other Abnormalities," the reporting of skin lesions generally increased from about 14 percent to 59 percent. The overall difference between the two examinations probably reflects a combination of factors, e.g., changes in disease, chance, the addition of new participants, and possible differences in clinical practice between the two groups of dermatologists.

The histologic categories of skin cancer (confirmed or suspected, any type), as examined by biopsies, showed a similarity between both groups.

SUMMARY AND CONCLUSIONS

Interval questionnaire data on the occurrence, time, and location of acne were analyzed to assess the possible historical diagnosis of chloracne. No significant difference was observed between groups for reported occurrence of acne, although the Ranch Hand cohort reported slightly more acne. The occurrence of acne relative to 1961 was comparable between groups. A marginally significant difference in the occurrence of post-1961 acne was found, with more Ranch Hands than Comparisons reporting acne strictly post-SEA. The duration of post-1961 acne was not significantly different between the two groups.

For participants with post-SEA acne, the spatial eyeglass distribution of acne (suggesting chloracne) was observed to be similar for the Ranch Hand and Comparison groups, both for individual sites and the combination of acne on the eyelids, ears, and temples. This analysis suggested that the occurrence of skin disease compatible with chloracne was not different in the two groups.

Analyses of the followup physical examination data, as with the Baseline examination, placed primary emphasis on six dermatologic disorders: comedones, acneiform lesions, acneiform scars, inclusion cysts, depigmentation, and hyperpigmentation. Secondary emphasis was given to 16 other minor conditions (generally not associated with chloracne) recorded at the physical examination. No significant findings occurred in any variable, as reflected in Table 14-28.

TABLE 14-28.

Overall Summary Results of Unadjusted and Adjusted Analyses of Questionnaire and Physical Examination Dermatological Variables

Variable	Unadjusted	Adjusted
Questionnaire		
Incidence of Acne		
Occurrence	NS	--
Relative to 1961	NS	--
Relative to SEA (Post-1961 Cases)	NS*	--
Duration of Acne	NS	NS
Location of Acne	NS	--
Physical Examination		
Comedones	NS	NS
Acneiform Lesions	NS	NS
Acneiform Scars	NS	NS
Depigmentation	NS	NS
Inclusion Cysts	NS	NS
Hyperpigmentation	NS	NS
Other Abnormalities	NS	NS
Dermatology Index	NS	****

NS: Not significant ($p>0.10$).

-- Analyses not performed.

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

****Group-by-covariate interaction.

No significant difference was found for any of these variables in the unadjusted analyses. The variable consisting of the 16 secondary conditions, labeled "other abnormalities," had the largest difference in the prevalence of abnormalities for the Ranch Hand cohort over the Comparison group (Est. RR: 1.08, 95% C.I.: [0.92,1.28], p=0.349), but the difference was clearly nonsignificant. The covariate effects of age, race, occupation, and the presence of pre-SEA acne were often profound with respect to the recorded dermatologic conditions.

The adjusted analyses closely mirrored the unadjusted analyses, with no significance noted between groups for any variable. Only one group-by-covariate interaction was observed in the adjusted analysis of the dermatology index, with a group-by-presence of pre-SEA acne interaction noted. However, further analysis of this interaction did not show an adverse effect in the Ranch Hand group.

Exposure index analyses did support dose-response relationships for some of the variables in certain occupational strata, but did not reveal a strong pattern of results suggesting a relationship between skin disease and herbicide exposure.

Overall, the followup examination results paralleled the Baseline findings. Although the followup examination detected more dermatologic abnormalities than those present at Baseline, slightly more abnormalities were found in the Comparisons, and most relative risks approached unity. The longitudinal analysis for the dermatology index showed no statistically significant differences between groups in the change in results from the Baseline to the followup examination.

In conclusion, none of the questionnaire results disclosed an increased likelihood of past chloracne in the Ranch Hands. The physical examination did not diagnose a current case of chloracne. The dermatological data were similar between the Ranch Hand and Comparison groups, and the longitudinal analysis of the dermatology index suggested equivalence between the Baseline and followup examination results.