Air Force Health Study

An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides

SAIC Team

Russell H. Roegner, Ph.D.
William D. Grubbs, Ph.D.
Michael B. Lustik, M.S.
Amy S. Brockman, M.S.
Scott C. Henderson, M.S.
David E. Williams, M.D., SCRF

Air Force Team

Col William H. Wolfe, M.D., M.P.H.
Joel E. Michalek, Ph.D.
Col Judson C. Miner, D.V.M., M.P.H.

Project Manager: R.H. Roegner
Statistical Task Manager: W.D. Grubbs
SAIC Quality Review Chair: W.F. Thomas
SAIC Editors: Cynthia A. Marut
Elisabeth M. Smeda

Program Manager: R.W. Ogershok

SCIENCE APPLICATIONS
INTERNATIONAL CORPORATION
8400 Westpark Drive
McLean, VA 22102

EPIDEMIOLOGY RESEARCH DIVISION
ARMSTRONG LABORATORY
HUMAN SYSTEMS DIVISION (AFSC)
Brooks Air Force Base, TX 78235

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SERUM DIOXIN ANALYSIS OF 1987 EXAMINATION RESULTS

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CHAPTER 10

GASTROINTESTINAL ASSESSMENT

INTRODUCTION

Background

In contrast to the wealth of research data available in animal models, there is relatively little information on the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the human digestive system. Though the pharmacokinetics of orally ingested TCDD in a human volunteer have been studied and reported (1), the pathologic lesions that have been studied in animals—gastric metaplasia with ulceration and ileitis, for example—have not been described in human populations where the principal route of exposure has been transcutaneous. Further, in two recent reports of extreme phenoxyherbicide toxicity by ingestion in three humans, the primary target organs were the central nervous system with associated coma and the musculoskeletal system with rhabdomyolysis and renal failure (2, 3).

The digestive system and, more specifically, the liver have been studied extensively and clearly defined as target organs for TCDD toxicity in numerous laboratory and domestic animals (4-8). Absorbed by the intestinal lymphatics and transported in the enterohepatic circulation by chylomicrons, TCDD ingested by rats (9-12) and guinea pigs (13) is preferentially stored in the liver. Hepatotoxic manifestations, which appear to be dose- and time-dependent, include cellular hypertrophy, parenchymal necrosis (principally centrilobular), and fatty degeneration (14-17). Much of the basic animal research into the mechanism of TCDD-induced hepatotoxicity has focused on the definition and function of the aryl hydroxylase (Ah) receptor, a stereospecific protein that is present in the cytosol of hepatic parenchymal cells (18-24). Capable of binding aromatic hydrocarbons, the species- and strain-specific Ah receptor mediates a broad range of biochemical/enzymatic reactions, many of which are dependent on the ferrocytochrome P-450 enzyme system (18, 25, 26).

A host of hepatic biochemical reactions have been studied related to TCDD toxicity including enhanced lipid peroxidation (27, 28, 29), hepatic prostaglandin synthetase activity (30), and inhibition of glutathione peroxidase (29). Results from several lines of biochemical investigation have created a bridge between animal and human studies including research into lipid (31-34) and porphyrin (35-39) metabolism. In rats, TCDD has been shown to increase the activity of glucuronyl transferase (40) which, in turn, has led to the use of urinary d-glucaric acid as a marker for TCDD exposure in this and other human epidemiologic studies (41, 42, 43).

Numerous human morbidity studies from the industrial sector have noted abnormal indices of liver function that in most cases were not associated with any other clinical evidence for liver or gastrointestinal disease (44-48). Further, in longer-term followup studies, abnormalities noted at the time of acute exposure appeared to resolve over time (49-53). A recent report, based on a more accurate estimate of prior TCDD exposure employing adipose tissue levels, found no abnormalities in standard liver function tests related to the body burden of dioxin (54).

In summary, basic research has provided valuable insight into the biochemical and molecular basis for TCDD toxicity in many mammalian species. But to date, clinical endpoints in the gastrointestinal system related to dioxin exposure in humans have been transient and not associated with any long-term sequelae.

More detailed summaries of the pertinent scientific literature for the gastrointestinal assessment can be found in the report of the previous analyses of the 1987 examination data (55).

Summary of Previous Analyses of the 1987 Examination Data

Overall, the gastrointestinal assessment did not find the health of the Ranch Hand group to be significantly different from the Comparison group. Group differences based on verified historical data from the questionnaire were not significant for eight categories of liver disease. No significant group difference was found for past or present occurrence of peptic ulcers. The prevalence of hepatomegaly diagnosed at the physical examination also was not significantly different between groups. The only significant finding from the laboratory examination variables was that the Ranch Hands had a higher mean alkaline phosphatase than the Comparisons. This also was noted at the 1985 examination. Group differences for the other laboratory variables (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [GGT], total bilirubin, direct bilirubin, lactic dehydrogenase [LDH], cholesterol, high-density lipoprotein [HDL], cholesterol-HDL ratio, triglycerides, and creatine kinase) were not significant. Stratified analyses to explore group-by-covariate interactions did not disclose any consistent pattern of significant group differences within any subgroup. The exposure index data often exhibited positive dose-response relationships, but results of the statistical analyses generally were not significant. The longitudinal analyses of AST, ALT, and GGT showed that the group differences did not change significantly between the Baseline examination and the 1987 examination.

Parameters of the Gastrointestinal Assessment

Dependent Variables

Questionnaire, physical examination, and laboratory data were used in the gastrointestinal assessment. The questionnaire data were organized by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) medical coding categories.

Questionnaire Data

During the health interview in 1987, each study participant was asked about the occurrence of hepatitis, jaundice, cirrhosis, enlarged liver, and other liver conditions. This self-reported information was combined with information from the Baseline and 1985 examinations and verified by medical record review. The verified results were then grouped into eight categories of disorders for analysis: viral hepatitis, acute and subacute necrosis of the liver, chronic liver disease and cirrhosis (alcohol-related and nonalcohol-related cirrhosis were analyzed separately), liver abscess and sequelae of chronic liver disease, other disorders of the liver (ICD codes 5730-5739, 7901, 7904, 7905, and 7948), jaundice (unspecified, not of the newborn), and hepatomegaly. Viral hepatitis was verified by serological testing. The abnormalities in the "other disorders" category were primarily

abnormal liver scans and unspecified disorders of the liver. Abnormal enzyme elevations and unspecified hepatitis (8 Ranch Hands, 13 Comparisons) also fell in this category. No analyses were done for acute and subacute necrosis of the liver or for liver abscess and sequelae of chronic liver disease because no Ranch Hands had these conditions. Two Comparisons had necrosis of the liver after service in Southeast Asia (SEA) and one had an abscess of the liver.

Information on the occurrence of skin bruises, patches, and sensitivity also was captured in the questionnaire. This self-reported information was combined with information from the Baseline and 1985 examinations, verified, and analyzed as part of the gastrointestinal assessment. This variable is considered a surrogate measure for a possible symptom of porphyria cutanea tarda. A verified ulcer variable based on gastric, duodenal, peptic, and gastrojejunal ulcers also was analyzed.

For each condition, participants with a pre-SEA diagnosis were excluded from the analysis.

Physical Examination Data

One variable from the 1987 physical examination, current hepatomegaly, was analyzed in the gastrointestinal assessment. This variable was coded as yes/no. Participants whose blood contained hepatitis B surface antigen (HB_SAg) were excluded from the analysis of current hepatomegaly.

Laboratory Examination Data

The 1987 examination emphasized evaluation of laboratory data, particularly for the hepatic function. Thirteen laboratory variables were analyzed: AST (U/L), ALT (U/L), GGT (U/L), alkaline phosphatase (U/L), d-glucaric acid (μM), total bilirubin (mg/dl), direct bilirubin (mg/dl), LDH (U/L), cholesterol (mg/dl), high-density lipoproteins (HDL in mg/dl), cholesterol-HDL ratio, triglycerides (mg/dl), and creatine kinase (U/L). The analyses of d-glucaric acid were based on urine collected during the 1985 examination and stored at -70°C. Each laboratory variable was analyzed in both continuous and discrete forms. All were dichotomized as high versus normal for the discrete analyses except HDL, which was dichotomized as low versus normal. Table 10-1 shows the ranges used to determine normal/abnormal cutpoints. A natural logarithm transformation was applied to all the variables except d-glucaric acid, which was analyzed on the square root scale. For direct bilirubin, the transformation was done after adding 0.1 to each value because several participants had levels of 0.0 mg/dl.

Participants whose blood contained HB_SAg and participants with body temperature greater than or equal to 100°F were excluded from the analysis of the laboratory variables. For d-glucaric acid, these exclusionary criteria were determined from the 1985 examination data.

Covariates

The gastrointestinal assessment examined the effects of covariates in the adjusted statistical analyses. Blood type was a candidate covariate for the adjusted analysis of verified ulcer. Age, race, current alcohol use, lifetime alcohol history, lifetime industrial

TABLE 10-1.

Statistical Analysis for the Gastrointestinal Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Viral Hepatitis	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC, OCC	U:LR A:LR
Acute and Subacute Necrosis of the Liver	Q/PE-V	D	Yes No	- -	- -
Chronic Liver Disease and Cirrhosis (Alcohol-Related)	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR A:LR
Chronic Liver Disease and Cirrhosis (Nonalcohol-Related)	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, CS, FT A:LR
Liver Abscess and Sequelae of Chronic Liver Disease	Q/PE-V	D	Yes No	- -	- -
Other Disorders of the Liver	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR A:LR
Jaundice (Unspecified)	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, CS, FT A:LR
Hepatomegaly	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR A:LR
Verified Ulcer	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC, BLOOD	U:LR A:LR
Skin Bruises, Patches, or Sensitivity	Q/PE-V	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR A:LR

TABLE 10-1. (Continued)

Statistical Analysis for the Gastrointestinal Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Current Hepatomegaly	PE	D	Yes No	AGE, RACE, ALC, DRKYR, IC, DC	U:LR A:LR
AST (U/L)	LAB	D/C	High: ≥48 Normal: ≤47	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM L:GLM
ALT (U/L)	LAB	D/C	High: ≥37 Normal: ≤36	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM L:GLM
GGT (U/L)	LAB	D/C	High: ≥86 Normal: ≤85	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM L:GLM
Alkaline Phosphatase (U/L)	LAB	D/C	High: ≥137 Normal: ≤136	AGE, RACE, WINE, LWINE, IC, DC	U:LR, GLM, CS, FT A:LR, GLM
D-Glucaric Acid (μM)	LAB	D/C	High: ≥99 Normal: ≤98	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM, CS, FT A:LR, GLM
Total Bilirubin (mg/dl)	LAB	D/C	High: ≥1.5 Normal: <1.5	AGE, RACE, ALC, DRKYR IC, DC	U:LR, GLM A:LR, GLM
Direct Bilirubin (mg/dl)	LAB	D/C	High: ≥0.41 Normal: ≤0.40	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM
LDH (U/L)	LAB	D/C	High: ≥191 Normal: ≤190	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM, CS, FT A:LR, GLM
Cholesterol (mg/dl)	LAB	D/C	High: ≥261 Normal: ≤260	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM

TABLE 10-1. (Continued)

Statistical Analysis for the Gastrointestinal Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
HDL (mg/dl)	LAB	D/C	Low: <30 Normal: ≥30	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM
Cholesterol-HDL Ratio	LAB	D/C	High: >5 Normal: ≤5	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM
Triglycerides (mg/dl)	LAB	D/C	High: ≥321 Normal: ≤320	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM
Creatine Kinase (U/L)	LAB	D/C	High: ≥233 Normal: ≤232	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Blood (BLOOD)	MIL	D	A B AB O
Age (AGE)	MIL	D/C	Born ≥1942 Born <1942
Race (RACE)	MIL	D	Black Non-Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew

TABLE 10-1. (Continued)

Statistical Analysis for the Gastrointestinal Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Current Alcohol Use (ALC) (drinks/day)	Q-SR	D/C	0-1 >1-4 >4
Lifetime Alcohol History (DRKYR) (drink-years)	Q-SR	D/C	0 >0-40 >40
Current Wine Use (WINE) (drinks of wine/day)	Q-SR	D/C	0 >0
Lifetime Wine History (LWINE) (wine-years)	Q-SR	D/C	0 >0
Industrial Chemical Exposure (IC)	Q-SR	D	Yes No
Degreasing Chemical Exposure (DC)	Q-SR	D	Yes No

Abbreviations

Data Source: LAB--1987 SCRF laboratory results
MIL--Air Force military records
PE--1987 SCRF physical examination
Q/PE-V--1987 questionnaire and physical examination (verified)
Q-SR--1987 questionnaire (self-reported) [1985 questionnaire when used with d-glucaric acid]

Data Form: D--Discrete analysis only
D/C--Discrete and continuous analyses for dependent variables; appropriate form for analysis (either discrete or continuous) for covariates

Statistical Analyses: U--Unadjusted analyses
A--Adjusted analyses
L--Longitudinal analyses

Statistical Methods: GLM--General linear models analysis
LR--Logistic regression analysis
CS--Chi-square contingency table test
FT--Fisher's exact test

chemical exposure, and lifetime degreasing chemical exposure were candidate covariates for the adjusted analyses of all of the laboratory variables except alkaline phosphatase. For alkaline phosphatase, current wine consumption was used instead of current alcohol use, and lifetime wine history was used instead of lifetime alcohol history since wine consumption showed a strong negative association with alkaline phosphatase in the 1985 examination. Because of a strong association, occupation was used as a covariate for the hepatitis analyses.

The lifetime alcohol history and current alcohol use covariates were based on self-reported information from the questionnaire. For lifetime alcohol history, the respondent's average daily alcohol consumption was determined for various drinking stages throughout his lifetime, and an estimate of the corresponding total number of drink-years (1 drink-year is the equivalent of drinking 1.5 ounces of 80-proof alcoholic beverage per day for 1 year) was derived. The current alcohol use covariate was based on the average drinks per day for the month prior to completing the questionnaire.

Age, current alcohol use, and lifetime alcohol history were treated as continuous variables for all adjusted analyses and were categorized to explore interactions, which are presented in Appendix Table I-1. Current wine use and lifetime wine history were treated as continuous variables for the adjusted alkaline phosphatase analyses, and were similarly categorized for interaction exploration. Degreasing chemical exposure and industrial chemical exposure were categorized for all analyses. The cutpoints used for categorization are specified in Table 10-1. In discussing the alcohol-related covariates, the terms light, moderate, and heavy are sometimes used to describe the current drinking habits of the participants; for lifetime alcohol use, never replaces light. These distinctions correspond to the three drinking categories in Table 10-1 for current alcohol use and lifetime alcohol history.

Relation to Baseline, 1985, and 1987 Studies

The verified questionnaire data analyzed in the 1987 assessment were organized by ICD-9-CM medical coding categories. Ulcers were not analyzed in the Baseline report.

For the laboratory variables, the gastrointestinal assessment was expanded to include HDL, cholesterol-HDL ratio, and creatine kinase subsequent to the Baseline study. The statistical analysis of d-glucaric acid was added for the previous report and is based on data collected at the 1985 physical examination. All other laboratory variables analyzed in the 1987 examination were analyzed in the Baseline and 1985 studies.

The longitudinal assessment analyzed AST, ALT, and GGT.

Statistical Methods

The basic statistical analysis methods used in the gastrointestinal assessment are described in Chapter 4, Statistical Methods. The modeling strategy was modified for the adjusted analyses of the questionnaire and physical examination variables. For these variables, the stepwise model examined the covariate main effects only; it did not include pairwise covariate interactions or dioxin-by-covariate interactions. Also, the adjusted analyses for these variables always kept age in the final model, regardless of the significance level.

Table 10-1 summarizes the statistical analyses performed for the 1987 gastrointestinal assessment. The first part of this table identifies the dependent variables, source of the data, form(s) of the data, cutpoints, candidate covariates, and statistical methods. The second part of the table provides additional information on the candidate covariates. Abbreviations are used extensively in the body of the table and are defined in footnotes. Dependent variable and covariate data were missing for some participants. Table 10-2 summarizes the number of participants with missing data and the number who were excluded from analyses for medical reasons.

Three statistical models were used to examine the association between a dependent variable and serum dioxin levels. One model related a dependent variable to each Ranch Hand's initial dioxin value (extrapolated from current dioxin values using a first-order pharmacokinetic model). A second model related a dependent variable to each Ranch Hand's current serum dioxin value and each Ranch Hand's time since tour of duty in SEA. The phrase "time since tour" is often referred to as "time" in discussions of these results. Both of these models were implemented under the minimal and maximal assumptions (i.e., Ranch Hands with current dioxin above 10 ppt and above 5 ppt, respectively). The third model compared the dependent variable for Ranch Hands having current dioxin values categorized as unknown, low, and high with Comparisons having background levels. The contrast of the entire Ranch Hand group with the complete Comparison group can be found in the previous report of analyses of the 1987 examination (55). All three models were implemented with and without covariate adjustment. Chapter 4 provides a more detailed discussion of the models.

Appendix I-1 contains graphic displays of individual dependent variables versus initial dioxin for the minimal and maximal cohorts, and individual variables versus current dioxin for Ranch Hands and Comparisons. Appendix I-2 presents graphics for dioxin-by-covariate interactions as determined by various statistical models. A guide to assist in interpreting the graphics is found in Chapter 4.

RESULTS

Exposure Analysis

Questionnaire Variables

Viral Hepatitis

Preliminary screening analyses found that the incidence of hepatitis differed significantly among occupational categories ($p<0.001$). Enlisted flyers and enlisted groundcrew had a higher incidence than officers. This finding was independent of group membership. For Ranch Hands in the maximal cohort, 53.9 percent of enlisted flyers and 42.4 percent of enlisted groundcrew had a history of hepatitis in contrast to 28.6 percent for officers. The relative frequencies for Comparisons with background levels of dioxin (≤10 ppt) were 52.9, 46.5, and 29.6 percent for the enlisted flyers, enlisted groundcrew, and officer occupational categories. Because occupation also is associated highly with both current and initial levels of dioxin (enlisted groundcrew have the highest dioxin levels followed by enlisted flyers and officers, see Chapter 2, Dioxin Assay), an additional model that included occupation was examined in each analysis. Appendix Table I-2 presents the results of these analyses.

TABLE 10-2.

Number of Participants Excluded and With Missing Data for the Gastrointestinal Assessment

Variable	Variable Use	Assumption (Ranch Hands Only)		Categorized Current Dioxin	
		Minimal	Maximal	Ranch Hand	Comparison
D-Glucaric Acid (1985)	DEP	15	25	25	36
Current Alcohol Use	COV	3	5	5	0
Current Alcohol Use (1985)	COV	17	26	25	35
Current Wine Use	COV	4	5	5	1
Lifetime Alcohol History	COV	6	9	9	2
Lifetime Alcohol History (1985)	COV	35	51	52	53
Lifetime Wine History	COV	4	6	6	2
Blood Type	COV	2	4	5	2
Pre-SEA Viral Hepatitis	EXC	15	22	21	25
Pre-SEA Acute and Subacute Necrosis of the Liver	EXC	0	0	0	1
Pre-SEA Chronic Liver Disease and Cirrhosis (Alcohol-Related)	EXC	1	1	1	3
Pre-SEA Other Disorders of the Liver	EXC	1	4	3	9
Pre-SEA Jaundice	EXC	14	21	19	24
Pre-SEA Hepatomegaly	EXC	1	1	1	1
Pre-SEA Ulcer	EXC	7	18	19	22
Pre-SEA Skin Bruises, Patches, or Sensitivity	EXC	11	18	15	18
Positive HB_SAg	EXC	3	4	7	4
Temperature ≥100 at 1987 Laboratory Exam	EXC	1	1	1	3
Positive HB_SAg (1985)	EXC	1	1	2	3
Temperature ≥100 at 1985 Laboratory Exam	EXC	2	2	1	1

DEP--Dependent variable (missing data).
COV--Covariate (missing data).
EXC--Exclusion.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analysis did not find a significant association with hepatitis under the minimal assumption (Table 10-3 [a]: p=0.613), but the association was marginally significant under the maximal assumption (Table 10-3 [b]: Est. RR=1.11, p=0.051). The incidences of hepatitis were 32.8, 42.0, and 42.8 percent for the low, medium, and high initial dioxin categories of the maximal cohort. Adjusting for age and race, the relative risk of hepatitis was significantly more than 1 under both assumptions (Table 10-3 [c]: Adj. RR=1.19, p=0.028 for the minimal cohort; Table 10-3 [d]: Adj. RR=1.24, p<0.001 for the maximal cohort). However, the relative risk became nonsignificant after adding occupation to the model (Appendix Table I-2: p=0.912 under the minimal assumption and p=0.777 under the maximal assumption).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the association between current dioxin and hepatitis did not differ significantly between time since tour strata based on the unadjusted analyses (Table 10-3 [e] and [f]: p=0.588 and p=0.296, respectively). After adjustment for age and race, the current dioxin-by-time interaction remained nonsignificant for both assumptions (Table 10-3 [g] and [h]: p=0.370 and p=0.224), although the adjusted relative risk was significant for Ranch Hands with a later tour (time≤18.6: Adj. RR=1.30, p=0.046 for the minimal assumption; Adj. RR=1.33, p=0.002 for the maximal assumption). The percentages of these Ranch Hands with hepatitis in the low, medium, and high current dioxin categories were 34.7, 41.1, and 34.6 percent under the minimal assumption, and 27.6, 36.9, and 40.7 percent under the maximal assumption. Adjusting for age and race, the relative risk was of borderline significance under the maximal assumption for Ranch Hands with an early tour (time>18.6: Adj. RR=1.15, p=0.080). However, these findings became nonsignificant when occupation was included in the model.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of categorized current dioxin did not find an overall difference in the incidence of hepatitis among the four current dioxin categories (Table 10-3 [i]: 41.5%, 35.5%, 41.4%, and 44.2% for the background, unknown, low, and high current dioxin categories, p=0.179), although the relative risk for the unknown versus background contrast was marginally less than 1 (Est. RR=0.78, 95% C.I.: [0.59,1.01], p=0.062).

After adjusting for age, race, and industrial chemical exposure, the overall current dioxin effect became significant (Table 10-3 [j]: p=0.022). The relative risk for the unknown versus background contrast remained marginally less than 1 (Adj. RR=0.77, 95% C.I.: [0.58,1.01], p=0.061), while the adjusted relative risk for the high versus background contrast became significantly more than 1 (Adj. RR=1.42, 95% C.I.: [1.01,2.00], p=0.047). However, all contrasts became nonsignificant after including occupation in the model (Appendix Table I-2: p>0.25 for each contrast). Adjusting for age, race, and occupation, the relative risk for the high versus background contrast was reduced to 1.03 (95% C.I.: [0.72,1.47], p=0.859).

TABLE 10-3.

Analysis of Viral Hepatitis

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=506)	Low	126	36.5	1.04 (0.90,1.20)	0.613
	Medium	252	44.8		
	High	128	42.2		
b) Maximal (n=720)	Low	183	32.8	1.11 (1.00,1.24)	0.051
	Medium	357	42.0		
	High	180	42.8		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=506)	1.19 (1.02,1.40)	0.028	AGE (p<0.001) RACE (p=0.011)
d) Maximal (n=720)	1.24 (1.10,1.39)	<0.001	AGE (p<0.001) RACE (p=0.003)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-3. (Continued)

Analysis of Viral Hepatitis

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.588[b]
(n=506)	≤18.6	34.7 (72)	41.1 (124)	34.6 (52)	1.04 (0.82,1.33)	0.722[c]
	>18.6	46.3 (54)	47.3 (129)	44.0 (75)	0.96 (0.79,1.16)	0.672[c]
f) Maximal						0.296[b]
(n=720)	≤18.6	27.6 (105)	36.9 (187)	40.7 (81)	1.14 (0.96,1.35)	0.131[c]
	>18.6	44.6 (74)	43.9 (173)	47.0 (100)	1.01 (0.87,1.17)	0.879[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.370[b]	AGE (p<0.001)
(n=506)	≤18.6	1.30 (1.00,1.68)	0.046[c]	RACE (p=0.011)
	>18.6	1.12 (0.91,1.38)	0.267[c]	
h) Maximal			0.224[b]	AGE (p<0.001)
(n=720)	≤18.6	1.33 (1.11,1.60)	0.002[c]	RACE (p=0.002)
	>18.6	1.15 (0.98,1.35)	0.080[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 10-3. (Continued)

Analysis of Viral Hepatitis

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	761	41.5	All Categories		0.179
Unknown	335	35.5	Unknown vs. Background	0.78 (0.59,1.01)	0.062
Low	191	41.4	Low vs. Background	0.99 (0.72,1.37)	0.967
High	181	44.2	High vs. Background	1.12 (0.80,1.55)	0.512
Total	1,468				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	761	All Categories		0.022	AGE (p<0.001) RACE (p<0.001)
Unknown	335	Unknown vs. Background	0.77 (0.58,1.01)	0.061	IC (p=0.006)
Low	191	Low vs. Background	0.99 (0.71,1.38)	0.935	
High	181	High vs. Background	1.42 (1.01,2.00)	0.047	
Total	1,468				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Chronic Liver Disease and Cirrhosis (Alcohol-Related)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The relative risk was less than 1, but not significant, for both the unadjusted and adjusted analyses of alcohol-related chronic liver disease and cirrhosis (Table 10-4 [a-d]: $p>0.15$ for each analysis under both the minimal and maximal assumptions).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not significant under both the minimal (Table 10-4 [e]: $p=0.317$) and maximal (Table 10-4 [f]: $p=0.463$) assumptions in the unadjusted analyses of alcohol-related chronic liver disease and cirrhosis. Under both assumptions, the current dioxin-by-time interaction remained nonsignificant after covariate adjustment (Table 10-4 [g] and [h]: $p=0.200$ and $p=0.199$ for the minimal and maximal assumptions), although the adjusted relative risk for Ranch Hands with an early tour was marginally less than 1 (time>18.6: Adj. RR=0.64, $p=0.082$ under the minimal assumption; Adj. RR=0.72, $p=0.087$ under the maximal assumption).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of alcohol-related chronic liver disease did not differ significantly among the four current dioxin categories in either the unadjusted (Table 10-4 [i]: $p=0.475$) or adjusted (Table 10-4 [j]: $p=0.449$) analysis. None of the three Ranch Hand versus background contrasts was significant for either analysis ($p>0.20$ for each contrast).

Chronic Liver Disease and Cirrhosis (Nonalcohol-related)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the initial dioxin analyses of nonalcohol-related chronic liver disease and cirrhosis were not significant (Table 10-5 [a-d]: $p>0.25$ for the unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not evaluated because only one Ranch Hand with an early tour had nonalcohol-related chronic liver disease. The association between current dioxin and nonalcohol-related chronic liver disease and cirrhosis was not significant for Ranch Hands with a later tour in both the unadjusted minimal (Table 10-5 [e]: $p=0.553$) and maximal (Table 10-5 [f]: $p=0.807$) analyses. No adjusted analyses were done due to sparse data.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of nonalcohol-related chronic liver disease and cirrhosis did not differ significantly among current dioxin categories (Table 10-5 [g] and [h]: 0.9%, 0.9%, 1.5%, and 0.0% for the background, unknown, low, and high categories; $p=0.446$ and $p=0.226$ in the unadjusted and adjusted analyses).

TABLE 10-4.

Analysis of Chronic Liver Disease and Cirrhosis (Alcohol-Related)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=520)	Low	130	6.2	0.89 (0.62,1.29)	0.543
	Medium	259	2.7		
	High	131	6.1		
b) Maximal (n=741)	Low	185	4.9	0.91 (0.70,1.19)	0.488
	Medium	370	4.3		
	High	186	4.8		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=514)	0.76 (0.51,1.13)	0.164	AGE (p=0.575) ALC (p<0.001) DRKYR (p=0.005)
d) Maximal (n=732)	0.85 (0.64,1.12)	0.238	AGE (p=0.807) ALC (p<0.001) DRKYR (p=0.001)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-4. (Continued)

Analysis of Chronic Liver Disease and Cirrhosis (Alcohol-Related)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.317[b]
(n=520)	≤18.6	5.6 (72)	1.6 (127)	5.6 (54)	1.10 (0.60,2.02)	0.747[c]
	>18.6	8.6 (58)	3.8 (132)	5.2 (77)	0.74 (0.45,1.22)	0.236[c]
f) Maximal						0.463[b]
(n=741)	≤18.6	4.7 (106)	2.6 (190)	4.8 (83)	1.01 (0.65,1.55)	0.977[c]
	>18.6	6.3 (79)	5.6 (179)	4.8 (104)	0.82 (0.57,1.16)	0.259[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.200[b]	AGE (p=0.536)
(n=514)	≤18.6	1.08 (0.57,2.06)	0.810[c]	ALC (p<0.001)
	>18.6	0.64 (0.39,1.06)	0.082[c]	DRKYR (p=0.006)
h) Maximal			0.199[b]	AGE (p=0.912)
(n=732)	≤18.6	1.05 (0.67,1.64)	0.827[c]	ALC (p<0.001)
	>18.6	0.72 (0.50,1.05)	0.087[c]	DRKYR (p=0.002)

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 10-4. (Continued)

Analysis of Chronic Liver Disease and Cirrhosis (Alcohol-Related)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	3.3	All Categories		0.475
Unknown	345	4.6	Unknown vs. Background	1.42 (0.75,2.68)	0.286
Low	195	2.6	Low vs. Background	0.77 (0.29,2.02)	0.589
High	187	4.8	High vs. Background	1.47 (0.68,3.20)	0.330
Total	1,510				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	781	All Categories		0.449	AGE (p=0.862)
Unknown	342	Unknown vs. Background	1.51 (0.77,2.96)	0.229	ALC (p<0.001)
Low	193	Low vs. Background	0.96 (0.36,2.58)	0.935	DRKYR (p=0.008)
High	183	High vs. Background	1.72 (0.75,3.95)	0.202	DC (p=0.076)
Total	1,499				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 10-5.

Analysis of Chronic Liver Disease and Cirrhosis (Nonalcohol-Related)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.8	0.67 (0.24,1.86)	0.411
	Medium	260	1.2		
	High	131	0.0		
b) Maximal (n=742)	Low	185	0.5	0.88 (0.44,1.75)	0.711
	Medium	371	1.1		
	High	186	0.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	0.59 (0.21,1.69)	0.287	AGE (p=0.282)
d) Maximal (n=742)	0.79 (0.40,1.56)	0.487	AGE (p=0.105)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-5. (Continued)

Analysis of Chronic Liver Disease and Cirrhosis (Nonalcohol-Related)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						--
(n=521)	≤18.6	1.4 (72)	1.6 (128)	0.0 (54)	0.67 (0.18,2.48)	0.553[b]
	>18.6	0.0 (58)	0.8 (132)	0.0 (77)	--	--
f) Maximal						--
(n=742)	≤18.6	0.9 (106)	1.6 (191)	0.0 (83)	0.90 (0.39,2.09)	0.807[b]
	>18.6	0.0 (79)	0.6 (179)	0.0 (104)	--	--

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

--: Relative risk/confidence interval/p-value not given due to the sparse number of abnormalities.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 10-5. (Continued)

Analysis of Chronic Liver Disease and Cirrhosis (Nonalcohol-Related)

g) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	0.9	All Categories		0.446
Unknown	345	0.9	Unknown vs. Background	0.98 (0.25,3.80)	0.999
Low	196	1.5	Low vs. Background	1.73 (0.44,6.74)	0.642
High	187	0.0	High vs. Background	--	0.446
Total	1,514				

h) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	786	All Categories		0.226	AGE (p=0.430)
Unknown	345	Unknown vs. Background	1.00 (0.26,3.91)	0.997	
Low	196	Low vs. Background	1.72 (0.44,6.72)	0.434	
High	187	High vs. Background	--	--	
Total	1,514				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Other Disorders of the Liver

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, both the unadjusted and the adjusted initial dioxin analyses did not find a significant association with other disorders of the liver (Table 10-6 [a] and [c]: p=0.220 and p=0.245, respectively). However, the relative risk was marginally significant under the maximal assumption (Table 10-6 [b] and [d]: Est. RR=1.19, p=0.051 in the unadjusted analysis; Adj. RR=1.19, p=0.061 in the adjusted analysis). The incidences were 5.0, 10.5, and 10.8 percent for the low, medium, and high initial dioxin categories of the maximal cohort.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the association between current dioxin and other disorders of the liver did not differ significantly between time since tour strata (Table 10-6 [e-h]: p>0.30 for the unadjusted and adjusted analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis found a marginally significant difference among the percentages of participants with "other disorders of the liver" (Table 10-6 [i]: 7.1%, 5.9%, 9.2%, and 11.8% for the background, unknown, low, and high current dioxin categories, p=0.087). The high versus background relative risk was significantly more than 1 (Est. RR=1.75, 95% C.I.: [1.04,2.95], p=0.036). The adjusted analysis showed similar results. After adjusting for age and current alcohol use, the overall contrast remained marginally significant (Table 10-6 [j]: p=0.084) and the adjusted relative risk for the high versus background contrast remained significant (Adj. RR=1.78, 95% C.I.: [1.03,3.07], p=0.038).

Jaundice

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Initial dioxin was not associated significantly with jaundice in either the unadjusted or adjusted analyses (Table 10-7 [a-d]: p>0.45 for all minimal and maximal analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Both the unadjusted and adjusted current dioxin and time since tour analyses for jaundice did not find a significant current dioxin-by-time interaction (Table 10-7 [e-h]: p>0.30 for the minimal and maximal analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of categorized current dioxin found a marginally significant difference among the incidences of jaundice (Table 10-7 [i]: 2.2%, 3.3%, 0.0%, and 1.1% for the background, unknown, low, and high current dioxin categories, p=0.056) with significantly fewer cases in the low current dioxin category relative to the background category (p=0.042). The overall contrast was significant in the adjusted analysis (Table 10-7 [j]: p=0.014).

TABLE 10-6.

Analysis of Other Disorders of the Liver

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=520)	Low	129	9.3	1.15 (0.92,1.45)	0.220
	Medium	260	9.2		
	High	131	12.2		
b) Maximal (n=738)	Low	182	5.0	1.19 (1.00,1.41)	0.051
	Medium	370	10.5		
	High	186	10.8		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=520)	1.15 (0.91,1.45)	0.245	AGE (p=0.907)
d) Maximal (n=733)	1.19 (0.99,1.42)	0.061	AGE (p=0.794) ALC (p<0.001)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-6. (Continued)

Analysis of Other Disorders of the Liver

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.535[b]
(n=520)	≤18.6	4.2 (71)	8.6 (128)	9.3 (54)	1.22 (0.81,1.85)	0.338[c]
	>18.6	15.5 (58)	9.1 (132)	15.6 (77)	1.04 (0.79,1.39)	0.768[c]
f) Maximal						0.408[b]
(n=738)	≤18.6	5.7 (105)	5.3 (190)	10.8 (83)	1.26 (0.93,1.70)	0.143[c]
	>18.6	6.5 (77)	14.0 (179)	12.5 (104)	1.07 (0.86,1.33)	0.531[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.547[b]	AGE (p=0.633)
(n=520)	≤18.6	1.20 (0.78,1.83)	0.408[c]	
	>18.6	1.02 (0.76,1.38)	0.873[c]	
h) Maximal			0.329[b]	AGE (p=0.852)
(n=733)	≤18.6	1.26 (0.92,1.73)	0.150[c]	ALC (p<0.001)
	>18.6	1.04 (0.83,1.31)	0.716[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 10-6. (Continued)

Analysis of Other Disorders of the Liver

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	777	7.1	All Categories		0.087
Unknown	342	5.9	Unknown vs. Background	0.82 (0.48,1.38)	0.449
Low	196	9.2	Low vs. Background	1.33 (0.76,2.32)	0.319
High	187	11.8	High vs. Background	1.75 (1.04,2.95)	0.036
Total	1,502				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	777	All Categories		0.084	AGE (p=0.978) ALC (p<0.001)
Unknown	340	Unknown vs. Background	0.84 (0.49,1.44)	0.527	
Low	194	Low vs. Background	1.44 (0.82,2.53)	0.203	
High	186	High vs. Background	1.78 (1.03,3.07)	0.038	
Total	1,497				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 10-7.

Analysis of Jaundice (Unspecified)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=507)	Low	125	0.8	1.22 (0.52,2.86)	0.655
	Medium	255	0.4		
	High	127	0.8		
b) Maximal (n=721)	Low	183	2.2	0.83 (0.48,1.46)	0.507
	Medium	358	0.6		
	High	180	1.1		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=507)	1.39 (0.60,3.19)	0.467	AGE (p=0.168)
d) Maximal (n=721)	0.90 (0.50,1.62)	0.722	AGE (p=0.060)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-7. (Continued)

Analysis of Jaundice (Unspecified)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.344[b]
(n=507)	≤18.6	1.4 (72)	0.8 (126)	0.0 (52)	0.92 (0.23,3.59)	0.899[c]
	>18.6	0.0 (53)	0.0 (130)	1.4 (74)	2.21 (0.60,8.15)	0.235[c]
f) Maximal						0.426[b]
(n=721)	≤18.6	0.0 (105)	1.1 (189)	1.2 (81)	1.03 (0.42,2.56)	0.947[c]
	>18.6	5.4 (74)	0.0 (172)	1.0 (100)	0.62 (0.27,1.42)	0.260[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.454[b]	AGE (p=0.117)
(n=507)	≤18.6	1.25 (0.31,5.14)	0.754[c]	
	>18.6	2.44 (0.74,8.09)	0.144[c]	
h) Maximal			0.396[b]	AGE (p=0.088)
(n=721)	≤18.6	1.20 (0.46,3.11)	0.711[c]	
	>18.6	0.69 (0.29,1.62)	0.390[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 10-7. (Continued)

Analysis of Jaundice (Unspecified)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	762	2.2	All Categories		0.056
Unknown	335	3.3	Unknown vs. Background	1.49 (0.69,3.21)	0.412
Low	193	0.0	Low vs. Background	--	0.042
High	181	1.1	High vs. Background	0.49 (0.11,2.14)	0.514
Total	1,471				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	762	All Categories		0.014	AGE (p=0.111)
Unknown	335	Unknown vs. Background	1.46 (0.67,3.15)	0.339	
Low	193	Low vs. Background	--	--	
High	181	High vs. Background	0.57 (0.13,2.50)	0.453	
Total	1,471				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

The change in significance between the unadjusted and adjusted results was due more to the choice of statistical method than to adjustment for age. A Pearson's chi-square p-value is presented for the unadjusted analysis because of sparse data; a likelihood ratio chi-square p-value is presented for the adjusted analysis. The likelihood ratio chi-square p-value based on an unadjusted analysis (p=0.011) is comparable to the adjusted result.

Hepatomegaly

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Neither the unadjusted nor adjusted initial dioxin analyses of a post-SEA history of hepatomegaly were significant (Table 10-8 [a-d]: p>0.20 for all analyses under both the minimal and maximal assumptions).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the interaction between current dioxin and time since tour was not significant in either the unadjusted or adjusted analysis of hepatomegaly (Table 10-8 [e-h]: p>0.25 for each analysis). The adjusted maximal analysis showed a marginally significant increased risk of hepatomegaly for Ranch Hands with a later tour (time$\leq$18.6: Adj. RR=1.67, p=0.065). In this stratum, the percentages of hepatomegaly were 0.0, 2.6, and 3.6 percent for low, medium, and high current dioxin.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis, the percentages of participants with a verified history of hepatomegaly did not differ significantly among current dioxin categories (Table 10-8 [i]: 2.2%, 0.9%, 3.1%, and 2.7% for the background, unknown, low, and high categories, p=0.230). The adjusted analysis also did not show a significant overall difference (Table 10-8 [j]: p=0.136).

Ulcer

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, initial dioxin was not associated significantly with the incidence of ulcer (Table 10-9 [a-d]: p>0.10 for the unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not significant for either the unadjusted or adjusted analysis of ulcer under both the minimal and maximal assumptions (Table 10-9 [e-h]: p>0.80 for each analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of ulcer did not differ significantly among the four current dioxin categories in the unadjusted categorized current dioxin analysis (Table 10-9 [i]: 7.2%, 7.3%, 4.7%, and 8.7% for the background, unknown, low, and high categories, p=0.455). The overall contrast was also not significant after covariate adjustment (Table 10-9 [j]: p=0.408).

TABLE 10-8.

Analysis of Hepatomegaly

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=520)	Low	130	2.3	0.90 (0.55,1.46)	0.657
	Medium	259	3.4		
	High	131	0.0		
b) Maximal (n=741)	Low	185	1.1	1.13 (0.80,1.61)	0.502
	Medium	371	2.4		
	High	185	2.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=520)	1.01 (0.62,1.65)	0.954	AGE (p=0.028)
d) Maximal (n=741)	1.25 (0.87,1.80)	0.248	AGE (p=0.009)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-8. (Continued)

Analysis of Hepatomegaly

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.921[b]
(n=520)	≤18.6	2.8 (72)	4.7 (128)	0.0 (54)	0.93 (0.47,1.84)	0.830[c]
	>18.6	0.0 (58)	3.8 (131)	0.0 (77)	0.98 (0.48,1.98)	0.944[c]
f) Maximal						0.363[b]
(n=741)	≤18.6	0.0 (106)	2.6 (191)	3.6 (83)	1.37 (0.82,2.22)	0.266[c]
	>18.6	1.3 (79)	2.2 (179)	1.9 (103)	0.98 (0.57,1.66)	0.928[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.964[b]	AGE (p=0.013)
(n=517)	≤18.6	1.17 (0.58,2.38)	0.665[c]	
	>18.6	1.16 (0.58,2.31)	0.682[c]	
h) Maximal			0.298[b]	AGE (p=0.004)
(n=741)	≤18.6	1.67 (0.97,2.87)	0.065[c]	
	>18.6	1.12 (0.65,1.93)	0.678[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 10-8. (Continued)

Analysis of Hepatomegaly

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	785	2.2	All Categories		0.230
Unknown	345	0.9	Unknown vs. Background	0.40 (0.12,1.36)	0.142
Low	196	3.1	Low vs. Background	1.43 (0.56,3.67)	0.461
High	186	2.7	High vs. Background	1.25 (0.45,3.43)	0.667
Total	1,512				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	785	All Categories		0.136	AGE (p=0.001) ALC (p=0.035)
Unknown	345	Unknown vs. Background	0.39 (0.11,1.33)	0.131	
Low	196	Low vs. Background	1.47 (0.57,3.79)	0.430	
High	186	High vs. Background	1.69 (0.60,4.75)	0.323	
Total	1,512				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 10-9.

Analysis of Ulcer

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=514)	Low	128	5.5	1.12 (0.85,1.48)	0.430
	Medium	255	6.7		
	High	131	6.9		
b) Maximal (n=724)	Low	178	4.5	1.16 (0.94,1.43)	0.165
	Medium	360	6.4		
	High	186	7.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=514)	1.14 (0.86,1.52)	0.376	AGE (p=0.619)
d) Maximal (n=724)	1.18 (0.95,1.46)	0.143	AGE (p=0.595)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-9. (Continued)

Analysis of Ulcer

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.885[b]
(n=514)	≤18.6	5.6 (71)	4.0 (125)	7.4 (54)	1.10 (0.67,1.83)	0.703[c]
	>18.6	7.0 (57)	7.7 (130)	7.8 (77)	1.05 (0.74,1.50)	0.768[c]
f) Maximal						0.845[b]
(n=724)	≤18.6	2.9 (104)	4.2 (189)	9.9 (81)	1.14 (0.80,1.63)	0.460[c]
	>18.6	4.2 (72)	8.1 (174)	7.7 (104)	1.09 (0.83,1.44)	0.525[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.875[b]	AGE (p=0.771)
(n=514)	≤18.6	1.12 (0.67,1.89)	0.661[c]	
	>18.6	1.07 (0.74,1.53)	0.720[c]	
h) Maximal			0.840[b]	AGE (p=0.735)
(n=724)	≤18.6	1.16 (0.81,1.66)	0.430[c]	
	>18.6	1.10 (0.83,1.46)	0.487[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 10-9. (Continued)

Analysis of Ulcer

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	764	7.2	All Categories		0.455
Unknown	331	7.3	Unknown vs. Background	1.01 (0.61,1.66)	0.976
Low	193	4.7	Low vs. Background	0.63 (0.31,1.30)	0.211
High	185	8.7	High vs. Background	1.22 (0.68,2.18)	0.502
Total	1,473				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	764	All Categories		0.408	AGE (p=0.285) IC (p=0.145)
Unknown	331	Unknown vs. Background	1.03 (0.62,1.69)	0.922	
Low	193	Low vs. Background	0.62 (0.30,1.28)	0.195	
High	185	High vs. Background	1.24 (0.69,2.25)	0.468	
Total	1,473				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Skin Bruises, Patches, or Sensitivity

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, initial dioxin was not significantly associated with the incidence of skin bruises, patches, or sensitivity (Table 10-10 [a-d]: $p>0.45$ for the unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted current dioxin and time since tour analyses of skin bruises, patches, or sensitivity, the interaction between current dioxin and time was not significant under either the minimal (Table 10-10 [e]: $p=0.657$) or maximal (Table 10-10 [f]: $p=0.800$) assumption. The current dioxin-by-time interaction remained nonsignificant after adjustment for age and industrial chemical exposure (Table 10-10 [g] and [h]: $p=0.569$ under the minimal assumption and $p=0.741$ under the maximal assumption).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of skin bruises, patches, or sensitivity differed significantly among the current dioxin categories in the unadjusted analysis (Table 10-10 [i]: 18.4%, 25.8%, 27.8%, and 31.9% for the background, unknown, low, and high current dioxin categories, $p<0.001$). There was a highly significant increased risk of skin bruises, patches, or sensitivity in the three Ranch Hand current dioxin categories relative to the background category (unknown versus background: Est. RR=1.54, 95% C.I.: [1.14,2.09], $p=0.005$; low versus background: Est. RR=1.72, 95% C.I.: [1.19,2.47], $p=0.004$; high versus background: Est. RR=2.08, 95% C.I.: [1.45,2.98], $p<0.001$). The adjusted analysis displayed similar findings. The overall contrast was highly significant (Table 10-10 [j]: $p<0.001$), as was each Ranch Hand versus background contrast (unknown versus background: Adj. RR=1.56, 95% C.I.: [1.15,2.12], $p=0.005$; low versus background: Adj. RR=1.71, 95% C.I.: [1.19,2.46], $p=0.004$; high versus background: Adj. RR=2.20, 95% C.I.: [1.52,3.18], $p<0.001$).

Physical Examination Variable

Current Hepatomegaly

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, initial dioxin was not associated significantly with the prevalence of hepatomegaly diagnosed at the 1987 physical examination in either the unadjusted or adjusted analysis (Table 10-11 [a-d]: $p>0.25$ for all analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The association between current dioxin and hepatomegaly did not differ significantly between time since tour strata for both the unadjusted and adjusted analyses (Table 10-11 [e-h]: $p>0.75$ for the minimal and maximal analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis for hepatomegaly diagnosed at the 1987 physical examination found a marginally significant overall contrast (Table 10-11 [i]:

TABLE 10-10.

Analysis of Skin Bruises, Patches, or Sensitivity

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=510)	Low	125	28.8	1.00 (0.86,1.17)	0.999
	Medium	255	29.4		
	High	130	33.1		
b) Maximal (n=724)	Low	178	28.1	1.04 (0.93,1.17)	0.484
	Medium	361	28.3		
	High	185	31.9		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=510)	1.03 (0.87,1.21)	0.753	AGE (p=0.032) IC (p=0.090)
d) Maximal (n=724)	1.04 (0.92,1.18)	0.508	AGE (p=0.027) IC (p=0.008)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-10. (Continued)

Analysis of Skin Bruises, Patches, or Sensitivity

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.657[b]
(n=510)	≤18.6	26.9 (67)	31.8 (126)	31.5 (54)	1.06 (0.82,1.36)	0.659[c]
	>18.6	31.6 (57)	26.9 (130)	34.2 (76)	0.98 (0.80,1.21)	0.869[c]
f) Maximal						0.800[b]
(n=724)	≤18.6	24.3 (103)	31.5 (184)	31.7 (82)	1.08 (0.90,1.29)	0.396[c]
	>18.6	23.7 (76)	29.0 (176)	32.0 (103)	1.05 (0.89,1.23)	0.572[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.569[b]	AGE (p=0.024)
(n=510)	≤18.6	1.12 (0.86,1.46)	0.403[c]	IC (p=0.101)
	>18.6	1.02 (0.82,1.27)	0.880[c]	
h) Maximal			0.741[b]	AGE (p=0.018)
(n=724)	≤18.6	1.16 (0.81,1.66)	0.430[c]	IC (p=0.012)
	>18.6	1.10 (0.83,1.46)	0.487[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 10-10. (Continued)

Analysis of Skin Bruises, Patches, and Sensitivity

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	768	18.4	All Categories		<0.001
Unknown	334	25.8	Unknown vs. Background	1.54 (1.14,2.09)	0.005
Low	194	27.8	Low vs. Background	1.72 (1.19,2.47)	0.004
High	185	31.9	High vs. Background	2.08 (1.45,2.98)	<0.001
Total	1,481				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	768	All Categories		<0.001	AGE (p=0.006) DC (p=0.091)
Unknown	334	Unknown vs. Background	1.56 (1.15,2.12)	0.005	
Low	194	Low vs. Background	1.71 (1.19,2.46)	0.004	
High	185	High vs. Background	2.20 (1.52,3.18)	<0.001	
Total	1,481				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 10-11.

Analysis of Current Hepatomegaly

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=518)	Low	130	1.5	0.89 (0.50,1.59)	0.687
	Medium	258	2.7		
	High	130	0.0		
b) Maximal (n=738)	Low	184	0.5	1.23 (0.80,1.90)	0.361
	Medium	369	1.4		
	High	185	1.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=518)	0.95 (0.53,1.71)	0.861	AGE (p=0.353)
d) Maximal (n=738)	1.30 (0.83,2.02)	0.271	AGE (p=0.308)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 10-11. (Continued)

Analysis of Current Hepatomegaly

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.986[b]
(n=518)	≤18.6	1.4 (72)	4.0 (126)	0.0 (53)	0.99 (0.46,2.12)	0.973[c]
	>18.6	0.0 (58)	2.3 (132)	0.0 (77)	0.98 (0.39,2.43)	0.959[c]
f) Maximal						0.800[b]
(n=738)	≤18.6	0.0 (105)	1.6 (189)	3.7 (82)	1.41 (0.79,2.52)	0.244[c]
	>18.6	0.0 (79)	0.6 (179)	1.9 (104)	1.25 (0.61,2.57)	0.537[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.939[b]	AGE (p=0.219)
(n=518)	≤18.6	1.13 (0.51,2.51)	0.755[c]	
	>18.6	1.08 (0.44,2.67)	0.861[c]	
h) Maximal			0.756[b]	AGE (p=0.175)
(n=738)	≤18.6	1.59 (0.86,2.94)	0.137[c]	
	>18.6	1.37 (0.67,2.81)	0.389[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 10-11. (Continued)

Analysis of Current Hepatomegaly

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	782	1.4	All Categories		0.052
Unknown	341	0.0	Unknown vs. Background	--	0.036
Low	194	1.6	Low vs. Background	1.10 (0.30,3.98)	0.999
High	186	2.7	High vs. Background	1.94 (0.66,5.64)	0.350
Total	1,503				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	782	All Categories		0.006	AGE (p=0.057)
Unknown	341	Unknown vs. Background	--	--	
Low	194	Low vs. Background	1.11 (0.31,4.04)	0.869	
High	186	High vs. Background	2.42 (0.81,7.29)	0.115	
Total	1,503				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

p=0.052). The percentages of participants who had hepatomegaly at the physical examination were 1.4, 0.0, 1.6, and 2.7 percent for the background, unknown, low, and high current dioxin categories. There were significantly fewer cases of hepatomegaly in the unknown category than in the background category (p=0.036).

The overall contrast was significant after adjusting for age (Table 10-11 [j]: p=0.006). However, the change in significance between the unadjusted and adjusted results was due partly to the choice of statistical method. A Pearson's chi-square p-value is presented for the unadjusted analysis because of sparse data; a likelihood ratio chi-square p-value is presented for the adjusted analysis. The likelihood ratio chi-square p-value based on an unadjusted analysis (p=0.011) is similar to the adjusted finding.

Laboratory Variables

AST (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analysis of AST in its continuous form was not significant for either the minimal (Table 10-12 [a]: p=0.878) or maximal (Table 10-12 [b]: p=0.304) analysis.

Under the minimal assumption, the adjusted analysis found a significant initial dioxin-by-degreasing chemical exposure interaction (Table 10-12 [c]: p=0.042). Exploration of this interaction showed a nonsignificant positive association between AST and initial dioxin for Ranch Hands who had never been exposed to degreasing chemicals (Appendix Table I-1: p=0.121) that contrasted with a nonsignificant negative association between AST and initial dioxin for Ranch Hands who had been exposed to degreasing chemicals (p=0.180).

Excluding the initial dioxin-by-degreasing chemical interaction, the adjusted minimal analysis did not reveal a significant association between AST and initial dioxin (Table 10-12 [c]: p=0.767). The adjusted maximal analysis also did not show a significant initial dioxin effect (Table 10-12 [d]: p=0.369).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The association between current dioxin and AST did not differ significantly between time since tour strata based on the unadjusted analyses for both the minimal and maximal assumptions (Table 10-12 [e] and [f]: p=0.599 and p=0.758).

The interaction between current dioxin and time remained nonsignificant for the adjusted minimal analysis (Table 10-12 [g]: p=0.576), but the interaction among current dioxin, time, and current alcohol use was significant for the adjusted maximal analysis (Table 10-12 [h]: p=0.002). The current alcohol use covariate was dichotomized to explore the interaction. Stratified results showed that the current dioxin-by-time interaction was not significant for Ranch Hands who currently consume one alcoholic beverage per day or less (Appendix Table I-1: p=0.225). However, the interaction was significant for Ranch Hands who currently consume more than one drink per day (p=0.031). There was a significant negative

TABLE 10-12.
Analysis of AST (U/L) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	130	26.86	0.0018 (0.0116)	0.878
(n=517)	Medium	257	25.78		
(R^2<0.001)	High	130	26.01		
b) Maximal	Low	184	24.85	0.0087 (0.0085)	0.304
(n=737)	Medium	368	26.36		
(R^2=0.001)	High	185	25.98		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean[a]	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
c) Minimal	Low	130	27.14**	-0.0033 (0.0113)**	0.767**	INIT*DC (p=0.042)
(n=511)	Medium	253	26.15**			ALC*RACE (p=0.002)
(R^2=0.122)	High	128	26.20**			ALC*DRKYR (p=0.029)
d) Maximal	Low	182	24.73	0.0076 (0.0084)	0.369	AGE*RACE (p=0.032)
(n=728)	Medium	365	26.18			RACE*ALC (p=0.035)
(R^2=0.126)	High	181	25.64			RACE*IC (p=0.023)
						ALC*DRKYR (p=0.035)
						ALC*IC (p=0.035)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm AST versus log_2 dioxin.

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.
INIT: Log_2 (initial dioxin).

TABLE 10-12. (Continued)

Analysis of AST (U/L) (Continuous)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
e) Minimal						0.599[c]
(n=517)	≤18.6	25.59	25.11	24.97	0.0038 (0.0189)	0.840[d]
(R^2=0.012)		(72)	(126)	(53)		
	>18.6	28.65	26.50	26.55	-0.0090 (0.0154)	0.559[d]
		(58)	(131)	(77)		
f) Maximal						0.758[c]
(n=737)	≤18.6	25.49	24.85	25.53	0.0018 (0.0132)	0.889[d]
(R^2=0.009)		(105)	(189)	(82)		
	>18.6	24.23	27.72	26.73	0.0072 (0.0116)	0.532[d]
		(79)	(178)	(104)		

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Mean[a]/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
g) Minimal						0.576[c]	DC (p=0.083)
(n=511)	≤18.6	25.19	24.78	24.52	-0.0022 (0.0179)	0.904[d]	RACE*ALC (p<0.001)
(R^2=0.140)		(72)	(125)	(52)			RACE*IC (p=0.019)
	>18.6	28.30	26.52	26.33	-0.0150 (0.0150)	0.316[d]	ALC*DRKYR (p=0.020)
		(58)	(128)	(76)			
h) Maximal						****	CURR*TIME*ALC
(n=728)	≤18.6	****	****	****	****	****	(p=0.002)
(R^2=0.143)		(104)	(188)	(80)			DC (p=0.071)
	>18.6	****	****	****	****	****	AGE*RACE (p=0.010)
		(78)	(176)	(102)			RACE*IC (p=0.018)
							ALC*DRKYR (p<0.001)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm AST versus log_2 dioxin.

[c]Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

[d]Test of significance for slope different from 0 (current dioxin continuous, time categorized).

****Log_2 (current dioxin)-by-time-by-covariate interaction ($p \leq 0.01$); adjusted mean, adjusted slope, standard error, and p-value not presented.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.
CURR: Log_2 (current dioxin).
TIME: Time since tour.

TABLE 10-12. (Continued)

Analysis of AST (U/L) (Continuous)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Mean[a]	Contrast	Difference of Means (95% C.I.)[e]	p-Value[f]
Background	779	25.70	All Categories		0.276
Unknown	341	24.93	Unknown vs. Background	-0.77 --	0.120
Low	193	25.46	Low vs. Background	-0.24 --	0.704
High	186	26.20	High vs. Background	0.50 --	0.434
Total	1,499		(R^2=0.003)		

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Adj. Mean[a]	Contrast	Difference of Adj. Means (95% C.I.)[e]	p-Value[f]	Covariate Remarks
Background	779	26.37	All Categories		0.374	RACE (p=0.075) ALC (p<0.001)
Unknown	339	25.71	Unknown vs. Background	-0.66 --	0.189	
Low	191	26.32	Low vs. Background	-0.05 --	0.943	
High	185	26.90	High vs. Background	0.53 --	0.409	
Total	1,494		(R^2=0.045)			

[a]Transformed from natural logarithm scale.

[e]Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

[f]P-value is based on difference of means on natural logarithm scale.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.