

CHAPTER 15

ENDOCRINE ASSESSMENT

INTRODUCTION

Background

The essential role of membrane and intracellular receptors in human endocrine function has been firmly established and extensively studied (1). Though dioxin exposure has not been proven to have endocrine effects in humans, the mechanism of dioxin toxicity on the endocrine system in laboratory animals continues to generate considerable interest. Much of this basic research has focused on physicochemical properties of the dioxin-binding aryl hydrocarbon (Ah) receptor that is present in selected animal tissues. Several recent reports have established that thyroid hormones and dioxin have common receptor binding properties and provide a molecular basis for understanding the biotoxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on indices of thyroid function (2, 3).

Since the endocrine literature was summarized for the previous report of the 1987 examination (4) relatively little has been published on the toxic effects of TCDD on thyroid function and the mechanism of dioxin-induced hypothyroidism remains unclear. A recent study (5) has confirmed previous observations (6, 7) that dioxin-induced changes in thyroid indices (serum thyroxine [T₄] and triiodothyronine [T₃]) can be directionally different and that the wasting syndrome associated with acute dioxin toxicity can be partially modified by diet (8, 9). The modulating effect of the thyroid gland on fatty acid synthesis was the subject of another report (10).

The finding of physicochemical similarities between the dioxin-binding Ah and glucocorticoid (GRc) receptors in laboratory animals (11, 12) has prompted additional studies into the interaction of TCDD and other steroid hormones. In rats, lethal doses of TCDD were associated with hypoglycemic shock that appeared secondary to reduced gluconeogenesis (13). The marked increase in mortality associated with total adrenalectomy (but not selective adrenal medullectomy) in rats is prevented by corticosterone administration (14) and appears to be modulated by changes in the binding capacity of the hepatic cytosolic GRc receptor (15).

The association of TCDD toxicity with birth defects in female experimental animals continues to drive basic research into estrogen and androgen metabolism. Though the mechanisms may differ (16), TCDD and progesterone appear to have similar estrogen-antagonist effects in rats by reducing nuclear and cytosolic receptors for both estrogen and progesterone (17). In rats, lipid mobilization and peroxidation may provide a biochemical basis for the testicular atrophy and impaired spermatogenesis associated with TCDD toxicity (18), though it is clear that there are strain differences in mice (19). The effects of TCDD on estrogen receptors have been summarized in a recent review article (20). In humans, one study documented a 20 percent incidence of impaired glucose tolerance in association with industrial exposure to TCDD (21).

To date, research into the toxic effects of TCDD on the endocrine system might be summarized as an attempt to clarify cause and effect. It is therefore not surprising that the

path of investigation has led to the pituitary gland and the hypothalamus. Employing microsurgical techniques in female rats, TCDD toxicity was found to be aggravated by hypophysectomy with a sparing effect noted on administration of either corticosterone or thyroid hormone (22). Another study has defined a biochemical basis to explain the effect of TCDD on prolactin levels controlled by the adenohipophysis (23) in female rats.

More detailed summaries of the pertinent scientific literature for the endocrine assessment can be found in the report of the previous analyses of the 1987 examination data (4).

Summary of Previous Analyses of the 1987 Examination Data

The endocrinologic assessment did not disclose any statistically significant differences between the Ranch Hand and Comparison groups. The percentage of participants who indicated problems with current thyroid disease was similar between groups, as were the percentages of thyroid and testicular abnormalities determined by palpation at the physical examination. Of the six laboratory examination variables that were examined (triiodothyronine percent [T_3 %] uptake, thyroid stimulating hormone [TSH], follicle stimulating hormone (FSH), testosterone, 2-hour postprandial glucose, and a composite diabetes indicator), the Ranch Hand TSH mean was marginally higher than the Comparison TSH mean, a finding that was statistically significant at the 1985 examination. Ranch Hand and Comparison mean levels for the other laboratory variables, including testosterone, were similar. For all laboratory variables, the percentage of Ranch Hands with abnormal values was higher than the percentage of Comparisons with abnormal values, but none of these differences was statistically significant. Group differences for fasting glucose, analyzed in the gastrointestinal assessment, were also nonsignificant. Exposure index results generally did not support the presence of a herbicide effect. The enlisted groundcrew and officer cohorts exhibited increasing dose-response patterns for diabetes, but the associations were not significant. Conversely, the overall result for diabetes was significant for enlisted flyers, but was due to the presence of relatively more diabetics in the medium exposure category than in either the low or high categories. The longitudinal analyses for the T_3 % uptake, TSH, and testosterone did not show significant differences between groups in the changes over time.

Parameters of the 1987 Endocrine Assessment

Dependent Variables

Questionnaire, physical examination, and laboratory data collected in 1987 were used in the endocrine assessment.

Questionnaire Data

In both the review-of-systems and the health interval questionnaire, general screening questions on thyroid function and disease were posed to each participant. The review-of-systems contained five questions on current thyroid function: thyroid or goiter trouble, high thyroid level, low thyroid level, lump in throat, and taking thyroid medication. Responses to these five questions were combined into a single item, which was coded as "yes" if there was a positive response to any question. During the face-to-face health interview, each study participant was asked, "Since the date of the last interview, has a doctor told you for the first time that you had thyroid problems?" All affirmative responses to the interviewer-

administered questionnaire and the review-of-systems were verified by medical record review and added to previously reported and verified information on the thyroid function for each participant. Based on the verified data, history of thyroid disease (interviewer-administered) was classified as yes/no. Responses from both the self-administered and interviewer-administered questions were analyzed as measures of the endocrine function.

Participants with a pre-Southeast Asia (SEA) history of thyroid disease were excluded from the analysis of the verified history of thyroid disease variable.

Physical Examination Data

The physical examination of the endocrine function was limited to manual palpation of the thyroid gland and the testes. Thyroid abnormalities consisted of enlarged gland, tenderness, or presence of nodules. The results of the testicular examination were coded as abnormal if atrophy was noted by the examiner.

Participants with thyroidectomies were excluded from the analysis of the thyroid gland. For the analysis of the testes, participants with orchiectomies were excluded.

Laboratory Examination Data

The endocrine assessment from laboratory data consisted of the analysis of T₃ % uptake, TSH (μ IU/ml), FSH (mIU/ml), testosterone (ng/dl), fasting glucose (mg/dl), 2-hour postprandial glucose (mg/dl), and the composite diabetes indicator. The 100-gram glucose load for the postprandial assay was standardized by the use of Glucola®. The composite diabetes indicator was coded as yes for a verified history of diabetes or a 2-hour postprandial glucose of 200 mg/dl or more.

Except for the composite diabetes indicator, all laboratory variables were analyzed in both discrete and continuous forms. Continuous analyses for T₃ % uptake, TSH, FSH, fasting glucose, and 2-hour postprandial glucose were done after transforming the data to the natural logarithm scale. The continuous analyses of TSH only used data above the detection limit of 0.5 μ IU, and the transformation was applied to (TSH-0.4). A square root transformation was applied for all continuous analyses of testosterone. The cutpoints for the discrete analyses were based on Scripps Clinic and Research Foundation (SCRF) reference values. T₃ % uptake and TSH were classified as normal/abnormal high. FSH was categorized as abnormal low, normal, and abnormal high. The categories for testosterone were normal/abnormal low. No assayed Ranch Hands had an elevated testosterone level. Fasting glucose was categorized as normal/abnormal high. In the discrete analysis of 2-hour postprandial glucose, the results were coded as normal, impaired, and diabetic.

Participants with thyroidectomies and those taking thyroid medication were excluded from the analyses of T₃ % uptake and TSH. For testosterone, participants with orchiectomies and those taking testosterone medication were excluded. Participants whose blood contained HB_sAg and participants with body temperature greater than or equal to 100°F were excluded from the analysis of fasting glucose. Known diabetics (verified history) were excluded from the analysis of 2-hour postprandial glucose. Participants with a pre-SEA history of diabetes were excluded from the analyses of the composite diabetes indicator. No participants were excluded from the analyses of FSH.

Covariates

The endocrine assessment examined the effects of the covariates age, race, and personality type in the adjusted analyses. Personality type was used as a covariate to adjust for the effects of stress. Personality type was not used for the adjusted analyses of FSH and fasting glucose. In the adjusted analyses of testes, testosterone, 2-hour postprandial glucose, and the composite diabetes indicator, percent body fat was also a candidate covariate. In addition to age and race, current alcohol use, lifetime alcohol history, lifetime industrial chemical exposure, and lifetime degreasing chemical exposure were candidate covariates in the adjusted analysis of fasting glucose. Age, percent body fat, current alcohol use, and lifetime alcohol history were treated as continuous variables for all adjusted analyses. These covariates were categorized for presentation purposes, such as interaction summaries presented in Appendix N, Table N-1.

Personality type was determined from the Jenkins Activity Survey administered at the 1985 examination. This variable was derived from a discriminant function equation based on questions that best discriminate men judged to be type A from those judged as type B. Positive scores reflect the type A direction and negative scores the type B direction. This variable was dichotomized into type A and type B for all analyses. Because the Jenkins Activity Survey was not administered at the 1987 examination, participants at the 1987 examination who had not attended the 1985 examination had missing information for this covariate.

Percent body fat, a measure of the relative body mass (24) of an individual derived from height and weight recorded at the physical examination, was computed by the following formula:

$$\text{Percent Body Fat} = \frac{\text{Weight (kg)}}{[\text{Height (m)}]^2} \cdot 1.264 - 13.305.$$

In its discrete form, this variable was dichotomized as lean/normal ($\leq 25\%$) and obese ($> 25\%$).

The lifetime alcohol history and current alcohol use covariates were based on self-reported information from the questionnaire.

Relation to Baseline, 1985, and 1987 Examination Studies

Except for FSH, all variables analyzed in this report were analyzed in the 1985 study. Only T₃ % uptake, 2-hour postprandial glucose, and testosterone were analyzed at Baseline. In the previous report of the 1987 examination data, fasting glucose was analyzed in the gastrointestinal assessment.

Three variables were analyzed in the longitudinal analysis of the endocrine function: T₃ % uptake, TSH, and testosterone.

Statistical Methods

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

Percent body fat exhibited a significant positive association with dioxin (see Chapter 6, General Health Assessment). Consequently, clinical endpoints in the endocrine assessment may be related to dioxin due to the association between dioxin and percent body fat. To investigate this possibility, the dioxin effect was evaluated in the context of two models whenever percent body fat was retained in the final model. The results of the analysis adjusting for percent body fat are discussed and tabled in the text. Appendix Table N-2 displays additional results for the final model excluding percent body fat. If the final model included a dioxin-by-covariate interaction, Appendix Table N-3 shows stratified results for the interaction model without adjusting for percent body fat. In general, these followup analyses are only discussed if a change in the significance of the results occurred.

Table 15-1 lists the dependent variables, data source, data form(s) (discrete and/or continuous), cutpoints, candidate covariates, and statistical methods used in the evaluation of the endocrine system. 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. In addition to the medical exclusions discussed previously, some dependent variable and covariate data were missing. Table 15-2 summarizes missing and exclusionary data.

Three statistical models were used to examine the association between a clinical endpoint 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. 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 (4). All three models were implemented with and without covariate adjustment. Chapter 4 provides a more detailed discussion of the models.

Appendix N-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 N-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.

TABLE 15-1.

Statistical Analysis for the Endocrine Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Current Thyroid Function (Self-Administered)	Q-SR	D	Abnormal Normal	AGE, RACE, PERS	U:LR A:LR
History of Thyroid Disease (Interviewer-Administered)	Q/PE-V	D	Yes No	AGE, RACE, PERS	U:LR A:LR
Thyroid Gland	PE	D	Abnormal Normal	AGE, RACE, PERS	U:LR A:LR
Testes	PE	D	Abnormal Normal	AGE, RACE, PERS, %BFAT	U:LR A:LR
T ₃ % Uptake	LAB	D/C	Abnormal High: >35% Normal: ≤35%	AGE, RACE, PERS	U:LR, GLM A:LR, GLM L:GLM
Thyroid Stimulating Hormone (TSH) (μIU/ml)	LAB	D/C	Abnormal High: >3 Normal: ≤3	AGE, RACE, PERS	U:LR, GLM A:LR, GLM L:LR
Follicle Stimulating Hormone (FSH) (mIU/ml)	LAB	D/C	Abnormal Low: <1.6 Normal: 1.6-17.2 Abnormal High: >17.2	AGE, RACE	U:LL, GLM A:LL, GLM
Testosterone (ng/dl)	LAB	D/C	Abnormal Low: <260 Normal/High: ≥260	AGE, RACE, PERS, %BFAT	U:LR, GLM A:LR, GLM L:GLM
Fasting Glucose (mg/dl)	LAB	D/C	High: ≥111 Normal: ≤110	AGE, RACE, ALC, DRKYR, IC, DC	U:LR, GLM A:LR, GLM
2-Hour Postprandial Glucose (mg/dl)	LAB	D/C	Diabetic: ≥200 Impaired: 140-<200 Normal: <140	AGE, RACE, PERS, %BFAT	U:LL, GLM A:LL, GLM

TABLE 15-1. (Continued)

Statistical Analysis for the Endocrine Assessment

Dependent Variables (Continued)

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Composite Diabetes Indicator	Q/PE-V, LAB	D	Yes (Diabetic): Verified History or ≥200 mg/dl No: Otherwise	AGE, RACE, PERS, %BFAT	U:LR A:LR

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥1942 Born <1942
Race (RACE)	MIL	D	Black Non-Black
Personality Type (PERS)	PE (1985)	D	A Direction B Direction
Percent Body Fat (%BFAT)	PE	D/C	Obese: >25% Lean/Normal: ≤25%
Current Alcohol Use (ALC) (drinks/day)	Q-SR	C	--
Lifetime Alcohol History (DRKYR) (drink-years)	Q-SR	D/C	0 >0-40 >40
Industrial Chemical Exposure (IC)	Q-SR	D	Yes No
Degreasing Chemical Exposure (DC)	Q-SR	D	Yes No

TABLE 15-1. (Continued)

Statistical Analysis for the Endocrine Assessment

Abbreviations

Data Source:	LAB--1987 SCRF laboratory results MIL--Air Force military records PE--1987 SCRF physical examination PE (1985)--1985 SCRF physical examination Q-SR--1987 Family and Personal History questionnaire (self-reported) Q/PE-V--Questionnaire and physical examination (verified)
Data Form:	C--Continuous Analysis only 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 LL--Log-linear models analysis LR--Logistic regression analysis

TABLE 15-2.

**Number of Participants Excluded and With Missing Data
for the Endocrine Assessment**

Variable	Variable Use	Assumption (Ranch Hands Only)		Categorized Current Dioxin	
		Minimal	Maximal	Ranch Hand	Comparison
Current Thyroid Function (Self-Administered)	DEP	2	3	3	0
Testes	DEP	5	6	5	1
2-Hour Postprandial Glucose	DEP	16	18	17	9
Composite Diabetes Indicator	DEP	2	2	3	2
Personality Type	COV	15	25	27	35
Current Alcohol Use	COV	3	5	5	0
Lifetime Alcohol History	COV	6	9	9	2
Thyroidectomy	EXC	4	8	9	6
Taking Thyroid Medication	EXC	7	9	9	10
Orchiectomy	EXC	5	6	5	1
Verified History of Diabetes	EXC	52	62	49	44
Pre-SEA Thyroid Condition	EXC	4	7	7	3
Pre-SEA Diabetes	EXC	2	2	1	2
Positive HB _s Ag	EXC	3	4	7	4
Temperature \geq 100 at 1987 Laboratory Exam	EXC	1	1	1	3

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

RESULTS

Exposure Analysis

Questionnaire Variables

Current Thyroid Function (Self-Administered)

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

The prevalence of reported current thyroid abnormalities was not associated significantly with initial dioxin under both the minimal and maximal assumptions (Table 15-3 [a-d]: $p > 0.25$ for the unadjusted and adjusted analyses).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

The association between current dioxin and current thyroid function did not differ significantly between time since tour strata under either the minimal or maximal assumption (Table 15-3 [e-h]: $p > 0.40$ for the unadjusted and adjusted analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The percentage of participants who reported an abnormal thyroid condition did not differ significantly among the four current dioxin categories (Table 15-3 [i] and [j]: $p > 0.90$ for the unadjusted and adjusted analyses). The three Ranch Hand versus background contrasts also were not significant.

History of Thyroid Disease (Interviewer-Administered)

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

The minimal and maximal analyses for history of thyroid disease did not show a significant association with initial dioxin (Table 15-4 [a-d]: $p > 0.50$ for the unadjusted and adjusted analyses).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not significant for all analyses of history of thyroid disease (Table 15-4 [e-h]: $p > 0.30$ for the unadjusted and adjusted analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted and adjusted results of the categorized current dioxin analyses for history of thyroid disease were not significant (Table 15-4 [i] and [j]: $p > 0.25$ for all contrasts). There were fewer verified reports of a history of thyroid disease in the low (3.1%) and high (3.8%) current dioxin categories than in the unknown (5.6%) and background categories (5.0%), although these differences were not significant.

TABLE 15-3.
Analysis of Current Thyroid Function
(Self-Administered)

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)^a	p-Value
a) Minimal (n=519)	Low	130	3.8	0.83 (0.54,1.28)	0.378
	Medium	259	3.9		
	High	130	2.3		
b) Maximal (n=739)	Low	184	3.8	0.86 (0.64,1.15)	0.298
	Medium	371	4.6		
	High	184	2.7		
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.)^a		p-Value	Covariate Remarks	
c) Minimal (n=519)	0.84 (0.54,1.31)		0.439	AGE (p=0.538) RACE (p=0.127)	
d) Maximal (n=739)	0.87 (0.65,1.18)		0.363	AGE (p=0.599) RACE (p=0.086)	

^aRelative 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 15-3. (Continued)
Analysis of Current Thyroid Function
(Self-Administered)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=519)	≤18.6	4.2 (72)	4.7 (128)	1.9 (54)	0.73 (0.37,1.46)	0.437 ^b 0.373 ^c
	>18.6	0.0 (58)	4.6 (131)	2.6 (76)	1.03 (0.60,1.78)	0.909 ^c
f) Maximal (n=739)	≤18.6	3.8 (106)	4.2 (191)	3.6 (83)	0.89 (0.57,1.39)	0.933 ^b 0.611 ^c
	>18.6	3.8 (78)	4.5 (179)	2.9 (102)	0.87 (0.58,1.30)	0.497 ^c
Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a		p-Value	Covariate Remarks	
g) Minimal (n=519)	≤18.6	0.76 (0.37,1.54)		0.437 ^b 0.447 ^c	AGE (p=0.459) RACE (p=0.135)	
	>18.6	1.07 (0.62,1.85)		0.813 ^c		
h) Maximal (n=739)	≤18.6	0.91 (0.58,1.42)		0.960 ^b 0.669 ^c	AGE (p=0.608) RACE (p=0.086)	
	>18.6	0.89 (0.59,1.34)		0.588 ^c		

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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 15-3. (Continued)

**Analysis of Current Thyroid Function
(Self-Administered)**

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	3.8	All Categories		0.925
Unknown	344	4.4	Unknown vs. Background	1.15 (0.61,2.16)	0.667
Low	196	3.6	Low vs. Background	0.93 (0.40,2.16)	0.872
High	185	3.2	High vs. Background	0.84 (0.35,2.06)	0.711
Total	1,511				

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	786	All Categories		0.931	AGE (p=0.927)
Unknown	344	Unknown vs. Background	1.15 (0.61,2.16)	0.670	
Low	196	Low vs. Background	0.93 (0.40,2.16)	0.872	
High	185	High vs. Background	0.85 (0.35,2.09)	0.724	
Total	1,511				

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

TABLE 15-4.

**Analysis of History of Thyroid Disease
(Interviewer-Administered)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)^a	p-Value
a) Minimal (n=517)	Low	130	4.6	1.13 (0.79,1.62)	0.508
	Medium	258	3.1		
	High	129	3.9		
b) Maximal (n=735)	Low	184	4.3	1.03 (0.79,1.33)	0.833
	Medium	367	4.4		
	High	184	3.8		
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.)^a		p-Value	Covariate Remarks	
c) Minimal (n=517)	1.13 (0.78,1.64)		0.519	AGE (p=0.988)	
d) Maximal (n=735)	1.05 (0.80,1.37)		0.722	AGE (p=0.471)	

^aRelative 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 15-4. (Continued)
Analysis of History of Thyroid Disease
(Interviewer-Administered)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	2.8 (72)	3.9 (127)	0.0 (54)	0.79 (0.36,1.73)	0.347 ^b 0.553 ^c
	>18.6	6.9 (58)	2.3 (131)	6.7 (75)	1.19 (0.78,1.82)	0.414 ^c
f) Maximal (n=735)	≤18.6	0.9 (106)	3.7 (190)	2.4 (83)	0.97 (0.58,1.62)	0.882 ^b 0.898 ^c
	>18.6	9.0 (78)	5.1 (176)	4.9 (102)	0.92 (0.67,1.27)	0.626 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
g) Minimal (n=517)	≤18.6	0.77 (0.34,1.73)	0.341 ^b 0.527 ^c	AGE (p=0.791)
	>18.6	1.18 (0.76,1.83)	0.471 ^c	
h) Maximal (n=735)	≤18.6	0.97 (0.58,1.64)	0.883 ^b 0.920 ^c	AGE (p=0.867)
	>18.6	0.93 (0.67,1.30)	0.666 ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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 15-4. (Continued)
Analysis of History of Thyroid Disease
(Interviewer-Administered)

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	5.0	All Categories		0.513
Unknown	342	5.6	Unknown vs. Background	1.12 (0.64,1.97)	0.689
Low	194	3.1	Low vs. Background	0.61 (0.25,1.46)	0.266
High	185	3.8	High vs. Background	0.75 (0.33,1.71)	0.493
Total	1,504				

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	783	All Categories		0.583	AGE (p=0.177)
Unknown	342	Unknown vs. Background	1.11 (0.63,1.95)	0.725	
Low	194	Low vs. Background	0.61 (0.26,1.47)	0.271	
High	185	High vs. Background	0.81 (0.35,1.87)	0.627	
Total	1,504				

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

Physical Examination Variables

Thyroid Gland

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

The prevalence of thyroid abnormalities diagnosed at the physical examination was not associated significantly with initial dioxin (Table 15-5 [a-d]: $p > 0.40$ for all unadjusted and adjusted analyses).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

The association between thyroid gland abnormalities and current dioxin did not differ significantly between time since tour strata (Table 15-5 [e-h]: $p > 0.75$ for all analyses whether unadjusted or adjusted).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The percentage of thyroid gland abnormalities did not differ significantly among the four current dioxin categories for the unadjusted and adjusted analyses (Table 15-5 [i] and [j]: $p > 0.25$ for all unadjusted and adjusted contrasts).

Testes

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

In the unadjusted analyses, the prevalence of testes abnormalities was not significantly associated with initial dioxin under the minimal assumption (Table 15-6 [a]: $p = 0.243$), but the relative risk was marginally more than 1 under the maximal assumption (Table 15-6 [b]: Est. RR=1.27, $p = 0.091$). The percentage of testes abnormalities increased with initial dioxin under the maximal assumption (1.6%, 3.3%, and 4.8% for the low, medium, and high initial dioxin categories). Under the minimal assumption, the percentages were 2.3, 4.3, and 3.8 percent for the low, medium, and high initial dioxin categories.

Adjusting for age and percent body fat, initial dioxin was significantly associated with an increase in testes abnormalities for both the minimal ($p = 0.017$) and maximal ($p = 0.003$) cohorts (Table 15-6 [c] and [d]: Adj. RR=1.61 for both).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the association between current dioxin and testes abnormalities did not differ significantly between time since tour strata (Table 15-6 [e-h]: $p > 0.10$ for the unadjusted and adjusted analyses). Although not significantly different, the relative risk was larger for Ranch Hands with a later tour than for those with an early tour for each cohort. The adjusted relative risk was significant for Ranch Hands with a later tour (time ≤ 18.6 : Adj. RR=2.59, $p = 0.006$ for the minimal cohort, Adj. RR=2.03, $p = 0.007$ for the maximal cohort). Under the maximal assumption, the adjusted relative risk was marginally significant for Ranch Hands with an early tour (time > 18.6 : Adj. RR=1.46, $p = 0.058$).

TABLE 15-5.
Analysis of Thyroid Gland

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.) ^a	p-Value
a) Minimal (n=517)	Low	130	26.2	0.97 (0.82,1.14)	0.712
	Medium	260	29.6		
	High	127	22.8		
b) Maximal (n=734)	Low	183	22.4	1.04 (0.92,1.17)	0.553
	Medium	369	28.5		
	High	182	24.2		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
c) Minimal (n=517)	0.98 (0.82,1.15)	0.771	AGE (p=0.784)
d) Maximal (n=734)	1.05 (0.93,1.19)	0.436	AGE (p=0.336)

^aRelative 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 15-5. (Continued)

Analysis of Thyroid Gland

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	23.6 (72)	28.9 (128)	18.9 (53)	0.94 (0.72,1.24)	0.887 ^b 0.679 ^c
	>18.6	32.8 (58)	28.0 (132)	27.0 (74)	0.97 (0.78,1.20)	0.766 ^c
f) Maximal (n=734)	≤18.6	19.8 (106)	28.8 (191)	22.0 (82)	1.01 (0.84,1.22)	0.754 ^b 0.916 ^c
	>18.6	24.7 (77)	28.8 (177)	25.7 (101)	1.05 (0.89,1.24)	0.548 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
g) Minimal (n=517)	≤18.6	0.95 (0.72,1.25)	0.890 ^b 0.697 ^c	AGE (p=0.958)
	>18.6	0.97 (0.78,1.21)	0.784 ^c	
h) Maximal (n=734)	≤18.6	1.03 (0.85,1.25)	0.754 ^b 0.783 ^c	AGE (p=0.367)
	>18.6	1.07 (0.90,1.26)	0.432 ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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 15-5. (Continued)**Analysis of Thyroid Gland****i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted**

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	780	27.7	All Categories		0.565
Unknown	340	26.2	Unknown vs. Background	0.93 (0.69,1.24)	0.600
Low	196	30.1	Low vs. Background	1.12 (0.80,1.58)	0.503
High	183	24.0	High vs. Background	0.83 (0.57,1.20)	0.318
Total	1,499				

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	780	All Categories		0.530	AGE (p=0.502)
Unknown	340	Unknown vs. Background	0.93 (0.70,1.24)	0.620	
Low	196	Low vs. Background	1.12 (0.80,1.58)	0.506	
High	183	High vs. Background	0.81 (0.56,1.18)	0.276	
Total	1,499				

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

TABLE 15-6.
Analysis of Testes

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.) ^a	p-Value
a) Minimal (n=516)	Low	128	2.3	1.24 (0.87,1.75)	0.243
	Medium	257	4.3		
	High	131	3.8		
b) Maximal (n=736)	Low	184	1.6	1.27 (0.97,1.66)	0.091
	Medium	366	3.3		
	High	186	4.8		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
c) Minimal (n=516)	1.61 (1.11,2.33)	0.017	AGE (p<0.001) %BFAT (p=0.049)
d) Maximal (n=736)	1.61 (1.20,2.18)	0.003	AGE (p<0.001) %BFAT (p=0.031)

^aRelative 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 15-6. (Continued)

Analysis of Testes

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=516)	≤18.6	1.4 (71)	4.7 (127)	1.9 (54)	1.49 (0.82,2.68)	0.303 ^b 0.189 ^c
	>18.6	5.3 (57)	3.1 (130)	5.2 (77)	1.00 (0.62,1.61)	0.987 ^c
f) Maximal (n=736)	≤18.6	1.9 (105)	1.6 (189)	7.2 (83)	1.33 (0.86,2.07)	0.536 ^b 0.200 ^c
	>18.6	2.5 (79)	4.0 (176)	3.8 (104)	1.11 (0.77,1.61)	0.571 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
g) Minimal (n=516)	≤18.6	2.59 (1.30,5.12)	0.121 ^b 0.006 ^c	AGE (p<0.001) %BFAT (p=0.043)
	>18.6	1.36 (0.83,2.23)	0.223 ^c	
h) Maximal (n=736)	≤18.6	2.03 (1.21,3.39)	0.311 ^b 0.007 ^c	AGE (p<0.001) %BFAT (p=0.033)
	>18.6	1.46 (0.99,2.17)	0.058 ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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 15-6. (Continued)

Analysis of Testes

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

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	785	2.9	All Categories		0.296
Unknown	343	2.6	Unknown vs. Background	0.89 (0.41,1.95)	0.776
Low	193	2.1	Low vs. Background	0.70 (0.24,2.05)	0.517
High	187	5.3	High vs. Background	1.87 (0.88,4.00)	0.106
Total	1,508				

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		0.010	AGE (p<0.001) RACE (p=0.079) %BFAT (p=0.010)
Unknown	343	Unknown vs. Background	0.75 (0.33,1.69)	0.486	
Low	193	Low vs. Background	0.76 (0.25,2.29)	0.627	
High	187	High vs. Background	3.80 (1.67,8.63)	0.001	
Total	1,508				

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

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of testes abnormalities did not differ significantly among current dioxin categories in the unadjusted analysis (Table 15-6 [i]: $p=0.296$). The high current dioxin category contained the highest percentage of abnormalities (2.9%, 2.6%, 2.1%, and 5.3% for the background, unknown, low, and high current dioxin categories).

After adjusting for age, race, and percent body fat, the overall contrast became significant (Table 15-6 [j]: $p=0.010$). The high versus background contrast was highly significant (Adj. RR=3.80, 95% C.I.: [1.67,8.63], $p=0.001$). The adjusted relative risks for the unknown versus background and low versus background contrasts were less than 1 and not significant.

Laboratory Examination Variables

T₃ % Uptake (Continuous)

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

T₃ % uptake exhibited a statistically significant negative association with initial dioxin in both the unadjusted minimal ($p=0.042$) and maximal ($p=0.002$) analyses (Table 15-7 [a] and [b]). The unadjusted mean T₃ % uptake decreased with initial dioxin for both cohorts (minimal: 30.54, 30.29, and 30.03 percent for the low, medium, and high initial dioxin categories; maximal: 30.66, 30.53, and 29.99 percent for the corresponding categories).

A significant negative association remained for both cohorts after adjusting for age, race, and personality type (Table 15-7 [c] and [d]: $p=0.034$ and $p=0.003$ for the minimal and maximal cohorts).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

The association of current dioxin and T₃ % uptake differed marginally between time since tour strata based on the unadjusted minimal analysis (Table 15-7 [e]: $p=0.060$), but the interaction between current dioxin and time was not significant for the unadjusted maximal analysis (Table 15-7 [f]: $p=0.119$). Both analyses showed a significant negative slope between T₃ % uptake and current dioxin for participants whose time since tour was more than 18.6 years (minimal: $p=0.016$; maximal: $p=0.003$). By contrast, the association for individuals whose time since tour was no more than 18.6 years was not significant for either cohort (minimal: $p=0.650$; maximal: $p=0.593$).

After adjusting for age, race, and personality type, the interaction between current dioxin and time was significant for the minimal analysis (Table 15-7 [g]: $p=0.015$) and marginally significant for the maximal analysis (Table 15-7 [h]: $p=0.058$). A significant negative slope between T₃ % uptake and current dioxin was evident for participants with an early tour (time > 18.6 years: $p=0.004$ and $p=0.002$ for the minimal and maximal assumptions), but the slope was not significant for Ranch Hands with a later tour (time ≤ 18.6 years: $p > 0.45$ under the minimal and maximal assumptions). The adjusted mean T₃ % uptake decreased for individuals whose time since tour was more than 18.6 years (minimal:

TABLE 15-7.

**Analysis of T₃ % Uptake
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted						
Assumption	Initial Dioxin	n	Mean^a	Slope (Std. Error)^b	p-Value	
a) Minimal (n=512) (R ² =0.008)	Low	129	30.54	-0.0059 (0.0029)	0.042	
	Medium	256	30.29			
	High	127	30.03			
b) Maximal (n=728) (R ² =0.013)	Low	183	30.66	-0.0065 (0.0021)	0.002	
	Medium	365	30.53			
	High	180	29.99			

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean^a	Adj. Slope (Std. Error)^b	p-Value	Covariate Remarks
c) Minimal (n=498) (R ² =0.036)	Low	125	30.89	-0.0064 (0.0030)	0.034	AGE (p=0.022) RACE (p=0.087) PERS (p=0.025)
	Medium	250	30.72			
	High	123	30.37			
d) Maximal (n=704) (R ² =0.026)	Low	174	30.93	-0.0067 (0.0022)	0.003	AGE (p=0.033) RACE (p=0.136) PERS (p=0.069)
	Medium	355	30.85			
	High	175	30.22			

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm T₃ % uptake versus log₂ 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 15-7. (Continued)

**Analysis of T₃ % Uptake
(Continuous)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Mean ^a /(n) Current Dioxin			Slope (Std. Error) ^b	p-Value
		Low	Medium	High		
e) Minimal (n=512) (R ² =0.017)	≤18.6	30.29 (71)	30.58 (126)	30.43 (53)	0.0021 (0.0047)	0.060 ^c 0.650 ^d
	>18.6	30.87 (58)	29.96 (130)	29.83 (74)	-0.0093 (0.0038)	0.016 ^d
f) Maximal (n=728) (R ² =0.016)	≤18.6	30.73 (106)	30.52 (189)	30.46 (81)	-0.0018 (0.0033)	0.119 ^c 0.593 ^d
	>18.6	30.62 (77)	30.47 (175)	29.69 (100)	-0.0087 (0.0030)	0.003 ^d

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Mean ^a /(n) Current Dioxin			Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=498) (R ² =0.048)	≤18.6	30.59 (68)	31.03 (123)	30.87 (50)	0.0036 (0.0050)	0.015 ^c 0.465 ^d	AGE (p=0.045) RACE (p=0.061) PERS (p=0.015)
	>18.6	31.50 (57)	30.41 (127)	30.20 (73)	-0.0114 (0.0040)	0.004 ^d	
h) Maximal (n=704) (R ² =0.031)	≤18.6	31.01 (99)	30.81 (182)	30.76 (78)	-0.0011 (0.0035)	0.058 ^c 0.752 ^d	AGE (p=0.047) RACE (p=0.118) PERS (p=0.053)
	>18.6	31.00 (75)	30.85 (172)	29.93 (98)	-0.0097 (0.0031)	0.002 ^d	

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm T₃ % uptake versus log₂ dioxin.

^cTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^dTest of significance for slope equal to 0 (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 15-7. (Continued)

**Analysis of T₃ % Uptake
(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	772	30.65	All Categories		0.010
Unknown	338	30.66	Unknown vs. Background	0.01 --	0.947
Low	194	30.35	Low vs. Background	-0.30 --	0.133
High	181	30.03	High vs. Background	-0.62 --	0.002
Total	1,485		(R ² =0.008)		

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	772	30.65***	All Categories		0.005***	DXCAT*AGE (p=0.001)
Unknown	338	30.67***	Unknown vs. Background	0.02 --***	0.895***	
Low	194	30.36***	Low vs. Background	-0.29 --***	0.130***	
High	181	29.99***	High vs. Background	-0.66 --***	0.001***	
Total	1,485		(R ² =0.020)			

^aTransformed from natural logarithm scale.

^eDifference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

^fp-value is based on difference of means on natural logarithm scale.

***Categorized current dioxin-by-covariate interaction (p≤0.01); adjusted mean and p-value derived from a model fitted after deletion of this interaction.

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.
 DXCAT: Categorized current dioxin.

31.50, 30.41, and 30.20 percent; maximal: 31.00, 30.85, and 29.93 percent for low, medium, and high current dioxin).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of categorized current dioxin found that the mean T₃ % uptake differed significantly among categories (Table 15-7 [i]: p=0.010). The mean for the high current dioxin category was significantly less than the background mean (30.03 percent versus 30.65 percent, p=0.002). The mean for the unknown current dioxin category (30.66 percent) and the mean for the low current dioxin category (30.35 percent) were not significantly different from the background mean.

The adjusted analysis of T₃ % uptake detected a significant current dioxin-by-age interaction (Table 15-7 [j]: p=0.001). Age was dichotomized to explore the interaction and the current dioxin effect was examined within each age category. Appendix Table N-1 shows that the mean T₃ % uptake differed significantly among current dioxin categories for both age groups (born in or after 1942: p=0.030; born before 1942: p<0.001). The means for the background, unknown, low, and high current dioxin categories were 30.59, 30.83, 31.12, and 30.13 percent for participants born in or after 1942. For older participants, those born before 1942, the means were 30.69, 30.57, 29.82, and 29.87 percent for the corresponding categories. The interaction occurred partly because, in the younger age stratum, the mean for the low current dioxin category was marginally higher than the background mean (p=0.081), but in the older age stratum, this contrast was highly significant in the opposite direction (p<0.001). The mean for Ranch Hands in the high current dioxin category was marginally less than the background mean in the younger age stratum (p=0.083), and significantly less than the background mean in the older age stratum (p=0.009).

Excluding the interaction, the adjusted results were similar to the unadjusted findings. The overall association between current dioxin and T₃ % uptake was significant (Table 15-7 [j]: p=0.005) and the mean T₃ % uptake for the high current dioxin category was significantly less than the background mean (p=0.001).

T₃ % Uptake (Discrete)

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

Neither the unadjusted minimal nor the maximal analysis detected a significant association between abnormally high levels of T₃ % uptake and initial dioxin (Table 15-8 [a] and [b]: p=0.240 and p=0.158, respectively). The percentage of abnormally high T₃ % uptake values was lowest for the high initial dioxin category in both the minimal and maximal cohorts. This finding is consistent with the results of the model 1 analyses for T₃ % uptake treated as a continuous variable, which found a significant decreasing trend between T₃ % uptake and initial dioxin.

No significant association was found after adjusting for race for the minimal cohort (Table 15-8 [c]: p=0.312). No covariates were found to be associated with T₃ % uptake for

TABLE 15-8.
Analysis of T₃ % Uptake
(Discrete)

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) ^a	p-Value
a) Minimal (n=512)	Low	129	4.7	0.76 (0.47,1.23)	0.240
	Medium	256	3.1		
	High	127	1.6		
b) Maximal (n=728)	Low	183	3.8	0.80 (0.59,1.10)	0.158
	Medium	365	4.7		
	High	180	1.7		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
c) Minimal (n=512)	0.79 (0.48,1.28)	0.312	RACE (p=0.103)
d) Maximal (n=728)	0.80 (0.59,1.10)	0.158	--

^aRelative 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 15-8. (Continued)

**Analysis of T₃ % Uptake
(Discrete)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) <u>Current Dioxin</u>			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=512)	≤18.6	5.6 (71)	4.0 (126)	1.9 (53)	0.86 (0.46,1.63)	0.777 ^b 0.652 ^c
	>18.6	3.4 (58)	2.3 (130)	1.4 (74)	0.75 (0.35,1.60)	0.455 ^c
f) Maximal (n=728)	≤18.6	2.8 (106)	5.8 (189)	2.5 (81)	0.91 (0.60,1.39)	0.477 ^b 0.669 ^c
	>18.6	3.9 (77)	4.0 (175)	1.0 (100)	0.72 (0.43,1.20)	0.205 ^c
Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a		p-Value	Covariate Remarks	
g) Minimal (n=512)	≤18.6	0.92 (0.48,1.74)		0.718 ^b 0.788 ^c	RACE (p=0.088)	
	>18.6	0.76 (0.35,1.66)		0.492 ^c		
h) Maximal (n=728)	≤18.6	0.91 (0.60,1.39)		0.477 ^b 0.669 ^c	--	
	>18.6	0.72 (0.43,1.20)		0.205 ^c		

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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 15-8. (Continued)

**Analysis of T₃ % Uptake
(Discrete)**

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

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	772	3.9	All Categories		0.359
Unknown	338	4.4	Unknown vs. Background	1.15 (0.61,2.16)	0.668
Low	194	3.6	Low vs. Background	0.93 (0.40,2.14)	0.857
High	181	1.7	High vs. Background	0.42 (0.13,1.38)	0.152
Total	1,485				

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	772	All Categories		0.451**	DXCAT*AGE (p=0.028)
Unknown	338	Unknown vs. Background	1.14 (0.60,2.14)**	0.693**	
Low	194	Low vs. Background	0.93 (0.40,2.15)**	0.863**	
High	181	High vs. Background	0.45 (0.13,1.49)**	0.188**	
Total	1,485				

**Categorized current dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤ 10 ppt.
 Unknown (Ranch Hands): Current Dioxin ≤ 10 ppt.
 Low (Ranch Hands): $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$.
 High (Ranch Hands): Current Dioxin $> 33.3 \text{ ppt}$.

the maximal analysis, making the adjusted analysis result identical to the unadjusted result (Table 15-8 [d]: $p=0.158$).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the current dioxin-by-time since tour interaction was not significant in either the unadjusted or adjusted analysis of discretized T₃ % uptake (Table 15-8 [e-h]: $p>0.40$ for each analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis for current dioxin was not significant for discretized T₃ % uptake (Table 15-8 [i]: $p=0.359$). Of the four current dioxin categories, the percentage of abnormally high T₃ % uptake values was lowest for the high category (3.9%, 4.4%, 3.6%, and 1.7% for the background, unknown, low, and high categories).

A significant interaction between current dioxin and age ($p=0.028$) was found in the adjusted analysis, but stratified results did not reveal a significant Ranch Hand versus background contrast (Appendix Table N-1). After excluding the interaction, the results of the adjusted analysis paralleled the unadjusted findings, showing no significant results (Table 15-8 [j]: $p>0.15$ for all contrasts).

TSH (Continuous)

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

The minimal and maximal analyses did not reveal a significant association between TSH in its continuous form and initial dioxin (Table 15-9 [a-d]: $p>0.50$ for all unadjusted and adjusted analyses).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the association between current dioxin and TSH did not differ between time since tour strata (Table 15-9 [e-h]: $p>0.40$ for all unadjusted and adjusted analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of categorized current dioxin was not significant for TSH (Table 15-9 [i]: $p=0.275$). None of the Ranch Hand versus background contrasts was significant, although the mean TSH increased with current dioxin levels (0.964, 0.997, 1.023, and 1.032 $\mu\text{IU/ml}$ for the background, unknown, low, and high current dioxin categories).

The adjusted analysis was of borderline significance (Table 15-9 [j]: $p=0.053$). Adjusting for age, race, and personality type, the mean TSH for the high current dioxin category was significantly more than the background mean (1.026 $\mu\text{IU/ml}$ versus 0.920 $\mu\text{IU/ml}$, $p=0.010$).

TABLE 15-9.

**Analysis of TSH (μ IU/ml)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted						
Assumption	Initial Dioxin	n	Mean^a	Slope (Std. Error)^b	p-Value	
a) Minimal (n=431) (R ² <0.001)	Low	112	1.007	-0.0157 (0.0315)	0.618	
	Medium	209	1.037			
	High	110	0.995			
b) Maximal (n=608) (R ² <0.001)	Low	150	1.045	-0.0136 (0.0233)	0.560	
	Medium	301	1.015			
	High	157	1.013			
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean^a	Adj. Slope (Std. Error)^b	p-Value	Covariate Remarks
c) Minimal (n=431) (R ² =0.028)	Low	112	0.910	-0.0070 (0.0322)	0.827	AGE (p=0.026) RACE (p=0.021)
	Medium	209	0.939			
	High	110	0.911			
d) Maximal (n=588) (R ² =0.021)	Low	143	1.039	0.0035 (0.0241)	0.886	AGE (p=0.002) PERS (p=0.092)
	Medium	291	1.009			
	High	154	1.043			

^aTransformed from natural logarithm (X - 0.4) scale (only values above the detection limit of 0.4 used).

^bSlope and standard error based on natural logarithm (TSH - 0.4) versus log₂ 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 15-9. (Continued)

**Analysis of TSH ($\mu\text{IU/ml}$)
(Continuous)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Mean ^a /(n) Current Dioxin			Slope (Std. Error) ^b	p-Value
		Low	Medium	High		
e) Minimal (n=431) (R ² =0.005)	≤18.6	0.991 (62)	1.001 (105)	0.982 (43)	0.0066 (0.0522)	0.440 ^c 0.900 ^d
	>18.6	1.049 (50)	1.063 (105)	1.004 (66)	-0.0449 (0.0415)	0.279 ^d
f) Maximal (n=608) (R ² =0.002)	≤18.6	1.020 (87)	0.980 (160)	1.055 (67)	-0.0138 (0.0367)	0.834 ^c 0.707 ^d
	>18.6	1.061 (64)	1.045 (140)	1.015 (90)	-0.0240 (0.0319)	0.451 ^d

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean ^a /(n) Current Dioxin			Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=431) (R ² =0.030)	≤18.6	0.902 (62)	0.914 (105)	0.908 (43)	0.0178 (0.0531)	0.476 ^c 0.737 ^d	AGE (p=0.048) RACE (p=0.021)
	>18.6	0.920 (50)	0.957 (105)	0.913 (66)	-0.0292 (0.0425)	0.493 ^d	
h) Maximal (n=588) (R ² =0.022)	≤18.6	1.013 (82)	0.985 (153)	1.107 (65)	0.0120 (0.0383)	0.743 ^c 0.754 ^d	AGE (p=0.003) PERS (p=0.092)
	>18.6	1.045 (62)	1.024 (137)	1.042 (89)	-0.0041 (0.0327)	0.899 ^d	

^aTransformed from natural logarithm (X - 0.4) scale (only values above the detection limit of 0.4 used).

^bSlope and standard error based on natural logarithm TSH versus log₂ dioxin.

^cTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^dTest of significance for slope equal to 0 (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 15-9. (Continued)

**Analysis of TSH (μ IU/ml)
(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	641	0.964	All Categories		0.275
Unknown	278	0.997	Unknown vs. Background	0.033 --	0.328
Low	155	1.023	Low vs. Background	0.059 --	0.165
High	157	1.032	High vs. Background	0.068 --	0.113
Total	1,231		(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	618	0.920	All Categories		0.053	AGE (p<0.001) RACE (p=0.080)
Unknown	265	0.948	Unknown vs. Background	0.028 --	0.362	PERS (p=0.129)
Low	151	0.978	Low vs. Background	0.058 --	0.135	
High	154	1.026	High vs. Background	0.106 --	0.010	
Total	1,188		(R ² =0.042)			

^aTransformed from natural logarithm (X - 0.4) scale (only values above the detection limit of 0.4 used).

^eDifference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm (X - 0.4) scale.

^fp-value is based on difference of means on natural logarithm (X - 0.4) scale.

Note: Background (Comparisons): Current Dioxin \leq 10 ppt.

Unknown (Ranch Hands): Current Dioxin \leq 10 ppt.

Low (Ranch Hands): 15 ppt < Current Dioxin \leq 33.3 ppt.

High (Ranch Hands): Current Dioxin >33.3 ppt.

TSH (Discrete)

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

The unadjusted analyses for discretized TSH did not show a significant relationship with initial dioxin for either the minimal or maximal cohorts (Table 15-10 [a] and [b]: $p=0.373$ and $p=0.765$). The adjusted analyses were identical to the unadjusted analyses because no covariates were included in the final models.

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not significant for both the unadjusted minimal ($p=0.520$) and maximal ($p=0.423$) analyses of discretized TSH (Table 15-10 [e] and [f]). The adjusted minimal analysis was identical to the unadjusted analysis because no covariates were retained in the final model.

Under the maximal assumption, the adjusted analysis detected a significant interaction among current dioxin, time, and personality type ($p=0.022$). Stratifying by personality type, the current dioxin-by-time interaction was significant for type A Ranch Hands (Appendix Table N-1: $p=0.026$). The relative risk was marginally less than 1 for type A Ranch Hands whose time since tour was more than 18.6 years (Adj. RR=0.40, $p=0.089$). By contrast, the relative risk was greater than 1, but not significant, for type A Ranch Hands whose time since tour had been 18.6 years or less (Adj. RR=1.70, $p=0.256$). The interaction between current dioxin and time was not significant for type B Ranch Hands ($p=0.382$).

After deleting the interaction with personality type, the results of the adjusted maximal analysis were identical to the unadjusted findings because personality type was dropped from the model.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of abnormally high TSH levels did not differ significantly among current dioxin categories in both the unadjusted (Table 15-10 [i]: $p=0.531$) and adjusted (Table 15-10 [j]: $p=0.430$) analyses of categorized current dioxin.

FSH (Continuous)

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

FSH was not associated significantly with initial dioxin in either the unadjusted minimal ($p=0.331$) or maximal ($p=0.463$) analysis (Table 15-11 [a] and [b]). These findings did not change after covariate adjustment (Table 15-11 [c] and [d]: $p=0.642$ and $p=0.372$ for the minimal and maximal cohorts).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

The association between current dioxin and FSH was marginally different between time since tour strata in the unadjusted minimal analysis (Table 15-11 [e]: $p=0.068$), and significantly different between time strata in the unadjusted maximal analysis (Table 15-11 [f]: $p=0.014$). In both analyses, there was a significant negative association between FSH and current dioxin for Ranch Hands with a later tour (time \leq 18.6: $p=0.014$ and $p=0.007$ for the

TABLE 15-10.**Analysis of TSH
(Discrete)****Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted**

Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) ^a	p-Value
a) Minimal (n=512)	Low	129	0.8	1.23 (0.79,1.94)	0.373
	Medium	256	2.3		
	High	127	3.1		
b) Maximal (n=728)	Low	183	3.3	1.05 (0.75,1.48)	0.765
	Medium	365	1.6		
	High	180	2.8		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
c) Minimal (n=512)	1.23 (0.79,1.94)	0.373	--
d) Maximal (n=728)	1.05 (0.75,1.48)	0.765	--

^aRelative 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 15-10. (Continued)

**Analysis of TSH
(Discrete)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=512)	≤18.6	0.0 (71)	2.4 (126)	1.9 (53)	1.48 (0.65,3.36)	0.520 ^b 0.354 ^c
	>18.6	3.4 (58)	1.5 (130)	4.1 (74)	1.06 (0.60,1.88)	0.845 ^c
f) Maximal (n=704)	≤18.6	1.9 (106)	0.5 (189)	3.7 (81)	1.23 (0.67,2.24)	0.423 ^b 0.507 ^c
	>18.6	5.2 (77)	2.3 (175)	3.0 (100)	0.90 (0.58,1.41)	0.643 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
g) Minimal (n=512)	≤18.6	1.48 (0.65,3.36)	0.520 ^b 0.354 ^c	--
	>18.6	1.06 (0.60,1.88)	0.845 ^c	
h) Maximal (n=704)	≤18.6	1.23 (0.67,2.24)**	0.423** ^b 0.507** ^c	CURR*TIME*PERS (p=0.022)
	>18.6	0.90 (0.58,1.41)**	0.643** ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log₂ (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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: Log₂ (current dioxin).

TIME: Time since tour.

TABLE 15-10. (Continued)

**Analysis of TSH
(Discrete)**

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

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	772	1.8	All Categories		0.531
Unknown	338	2.7	Unknown vs. Background	1.48 (0.63,3.46)	0.364
Low	194	1.5	Low vs. Background	0.85 (0.24,2.99)	0.801
High	181	3.3	High vs. Background	1.86 (0.70,4.90)	0.212
Total	1,485				

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	772	All Categories		0.430	AGE (p=0.119)
Unknown	338	Unknown vs. Background	1.45 (0.62,3.40)	0.387	
Low	194	Low vs. Background	0.86 (0.24,3.02)	0.810	
High	181	High vs. Background	2.15 (0.80,5.79)	0.130	
Total	1,485				

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

TABLE 15-11.
Analysis of FSH (mIU/ml)
(Continuous)

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Mean ^a	Slope (Std. Error) ^b	p-Value
a) Minimal (n=521) (R ² =0.002)	Low	130	8.61	-0.0258 (0.0265)	0.331
	Medium	260	7.58		
	High	131	7.44		
b) Maximal (n=742) (R ² <0.001)	Low	185	7.70	-0.0145 (0.0197)	0.463
	Medium	371	7.96		
	High	186	7.56		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean ^a	Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
c) Minimal (n=521) (R ² =0.087)	Low	130	7.49	0.0122 (0.0263)	0.642	AGE (p<0.001) RACE (p=0.131)
	Medium	260	6.88			
	High	131	7.24			
d) Maximal (n=742) (R ² =0.084)	Low	185	7.60	0.0172 (0.0193)	0.372	AGE (p<0.001)
	Medium	371	7.67			
	High	186	8.25			

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm FSH versus log₂ 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 15-11. (Continued)

**Analysis of FSH (mIU/ml)
(Continuous)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Mean ^a /(n) Current Dioxin			Slope (Std. Error) ^b	p-Value
		Low	Medium	High		
e) Minimal (n=521) (R ² =0.016)	≤18.6	8.25 (72)	7.49 (128)	6.28 (54)	-0.1058 (0.0429)	0.068 ^c 0.014 ^d
	>18.6	8.86 (58)	7.78 (132)	8.32 (77)	-0.0043 (0.0351)	0.902 ^d
f) Maximal (n=742) (R ² =0.011)	≤18.6	8.24 (106)	7.87 (191)	6.60 (83)	-0.0819 (0.0305)	0.014 ^c 0.007 ^d
	>18.6	7.56 (79)	8.02 (179)	8.04 (104)	0.0184 (0.0270)	0.495 ^d

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Mean ^a /(n) Current Dioxin			Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=521) (R ² =0.092)	≤18.6	7.27 (72)	7.06 (128)	6.50 (54)	-0.0482 (0.0428)	0.088 ^c 0.260 ^d	AGE (p<0.001) RACE (p=0.108)
	>18.6	7.23 (58)	6.90 (132)	7.82 (77)	0.0433 (0.0348)	0.215 ^d	
h) Maximal (n=742) (R ² =0.093)	≤18.6	8.26 (106)	7.96 (191)	7.59 (83)	-0.0348 (0.0298)	0.011 ^c 0.243 ^d	AGE (p<0.001)
	>18.6	6.85 (79)	7.47 (179)	8.56 (104)	0.0643 (0.0264)	0.015 ^d	

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm FSH versus log₂ dioxin.

^cTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^dTest of significance for slope equal to 0 (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 15-11. (Continued)

**Analysis of FSH (mIU/ml)
(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	786	7.57	All Categories		0.602
Unknown	345	7.96	Unknown vs. Background	0.39 --	0.277
Low	196	7.77	Low vs. Background	0.20 --	0.636
High	187	7.36	High vs. Background	-0.21 --	0.639
Total	1,514		(R ² =0.001)		

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	786	7.50	All Categories		0.583	AGE (p<0.001)
Unknown	345	7.73	Unknown vs. Background	0.23 --	0.507	
Low	196	7.75	Low vs. Background	0.25 --	0.549	
High	187	8.08	High vs. Background	0.58 --	0.187	
Total	1,514		(R ² =0.088)			

^aTransformed from natural logarithm scale.

^eDifference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

^fP-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.

minimal and maximal analyses) in contrast to a nonsignificant association for Ranch Hands with an early tour.

After covariate adjustment, the current dioxin-by-time interaction remained marginally significant under the minimal assumption (Table 15-11 [g]: $p=0.088$) and significant under the maximal assumption (Table 15-11 [h]: $p=0.011$). However, the adjusted results for the individual time strata differed from the unadjusted findings. Under the maximal assumption, the association between FSH and current dioxin became significantly positive for Ranch Hands with an early tour (time>18.6: $p=0.015$), but for both assumptions, the association between FSH and current dioxin was no longer significant for Ranch Hands with a later tour.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The mean FSH did not differ significantly among the four current dioxin categories in the unadjusted analysis (Table 15-11 [i]: $p=0.602$). The adjusted analysis was also not significant (Table 15-11 [j]: $p=0.583$).

FSH (Discrete)

Model 1: Ranch Hands – Initial Dioxin (Categorized)

Under both the minimal and maximal assumptions, discretized FSH was not associated with categorized initial dioxin (Table 15-12 [a-d]: $p>0.10$ for the unadjusted and adjusted analyses).

Model 2: Ranch Hands – Current Dioxin (Categorized) and Time

The current dioxin-by-time since tour interaction was not significant for the unadjusted minimal analysis of discretized FSH (Table 15-12 [e]: $p=0.685$). However, under the maximal assumption, the interaction between current dioxin and time was marginally significant in the unadjusted analysis (Table 15-12 [f]: $p=0.053$). The interaction occurred partly because the low current dioxin category had the fewest abnormally high FSH levels for Ranch Hands with an early tour (time>18.6: 8.5%, 16.7%, and 13.0% for the low, medium, and high current dioxin categories), but it had the most abnormally high FSH values for Ranch Hands with a later tour (time≤18.6: 15.7%, 9.4%, and 5.6% for the low, medium, and high current dioxin categories). For Ranch Hands with an early tour, the risk of an abnormally high FSH level was significantly higher for individuals in the medium current dioxin category than for those in the low current dioxin category (time>18.6: Adj. RR=2.16, 95% C.I.: [1.04,4.47], $p=0.039$). For Ranch Hands with a later tour, the risk of an abnormally high FSH level was marginally less for the high current dioxin category versus the low current dioxin category (time≤18.6: Adj. RR=0.33, 95% C.I.: [0.10, 1.11], $p=0.074$).

Adjusting for age, the interaction between current dioxin and time remained nonsignificant for the minimal cohort, but the interaction was significant for the maximal cohort (Table 15-12 [g] and [h]: $p=0.710$ and $p=0.047$, respectively). For Ranch Hands with an early tour, the medium versus low contrast for abnormally high FSH was significant (Adj. RR=2.43, 95% C.I.: [1.16,5.06], $p=0.018$) and the high versus low contrast was marginally significant (Adj. RR=2.10, 95% C.I.: [0.87,5.09], $p=0.099$) under the maximal assumption. No contrasts were significant for Ranch Hands with a later tour.

TABLE 15-12.

Analysis of FSH
(Discrete)

Ranch Hands - Initial Dioxin (Categorized) - Unadjusted								
Assumption	Initial Dioxin	n	Percent			Initial Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
			Low	Normal	High			
a) Minimal (n=521)	Low	130	0.0	84.6	15.4	Overall [†]		0.144
	Medium	260	1.9	85.8	12.3	M vs. L ^a	--	--
	High	131	2.3	88.5	9.2	H vs. L ^a	--	--
						M vs. L ^b	0.79 (0.43,1.45)	0.445
						H vs. L ^b	0.57 (0.27,1.21)	0.143
b) Maximal (n=742)	Low	349	1.7	84.8	13.5	Overall [†]		0.765
	Medium	262	1.9	85.9	12.2	M vs. L ^a	1.10 (0.33,3.61)	0.876
	High	131	2.3	88.5	9.2	H vs. L ^a	1.30 (0.32,5.17)	0.714
						M vs. L ^b	0.90 (0.55,1.45)	0.654
						H vs. L ^b	0.65 (0.34,1.28)	0.215

Ranch Hands - Initial Dioxin (Categorized) - Adjusted

Assumption	Initial Dioxin Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) Minimal (n=521)	Overall [†]		0.481	AGE (p=0.005)
	M vs. L ^a	--	--	
	H vs. L ^a	--	--	
	M vs. L ^b	0.83 (0.45,1.53)	0.550	
	H vs. L ^b	0.69 (0.32,1.49)	0.348	
d) Maximal (n=742)	Overall [†]		0.982	AGE (p<0.001)
	M vs. L ^a	0.98 (0.30,3.22)	0.978	
	H vs. L ^a	0.91 (0.23,3.67)	0.898	
	M vs. L ^b	0.95 (0.58,1.54)	0.824	
	H vs. L ^b	0.81 (0.41,1.59)	0.536	

^aLow FSH contrasted with normal FSH.

^bHigh FSH contrasted with normal FSH.

[†]Overall test of independence of initial dioxin and FSH.

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

M vs. L: Medium initial dioxin category versus low initial dioxin category.

H vs. L: High initial dioxin category versus low initial dioxin category.

TABLE 15-12. (Continued)

Analysis of FSH
(Discrete)

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

Assumption	Time (Yrs.)	FSH Category	Percent/(n) Current Dioxin			Current Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
e) Minimal (n=521)	≤18.6	Low	0.0	2.3	3.7	C-by-Ta		0.685
		Normal	86.1	88.3	90.7	Overall†		0.144
		High	13.9	9.4	5.6	M vs. L ^b	--	--
			(72)	(128)	(54)	H vs. L ^b	--	--
						M vs. L ^c	0.66 (0.27,1.63)	0.367 ^d
						H vs. L ^c	0.39 (0.11,1.39)	0.147 ^d
	>18.6	Low	0.0	1.5	1.3	Overall†		0.649
		Normal	87.9	81.8	85.7	M vs. L ^b	--	--
		High	12.1	16.7	13.0	H vs. L ^b	--	--
			(58)	(132)	(77)	M vs. L ^c	1.47 (0.61,3.55)	0.389 ^d
						H vs. L ^c	1.10 (0.36,3.37)	0.871 ^d
f) Maximal (n=742)	≤18.6	Low	2.0	2.3	3.7	C-by-Ta		0.053
		Normal	82.3	88.3	90.7	Overall†		0.191
		High	15.7	9.4	5.6	M vs. L ^b	1.09 (0.24,4.86)	0.910 ^d
			(198)	(128)	(54)	H vs. L ^b	1.70 (0.31,9.26)	0.538 ^d
						M vs. L ^c	0.56 (0.28,1.13)	0.108 ^d
						H vs. L ^c	0.33 (0.10,1.11)	0.074 ^d
	>18.6	Low	1.3	1.5	1.3	Overall†		0.344
		Normal	90.2	81.8	85.7	M vs. L ^b	1.28 (0.19,8.80)	0.803 ^d
		High	8.5	16.7	13.0	H vs. L ^b	1.09 (0.11,11.21)	0.940 ^d
			(153)	(132)	(77)	M vs. L ^c	2.16 (1.04,4.47)	0.039 ^d
						H vs. L ^c	1.62 (0.68,3.86)	0.280 ^d

^aTest of significance of current dioxin-by-time interaction.

^bLow FSH contrasted with normal FSH.

^cHigh FSH contrasted with normal FSH.

^dTest of significance for relative risk equal to 1 (current dioxin and time categorized).

†Overall test of independence of current dioxin and FSH within time stratum.

--: Estimated relative risk, confidence interval, and 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: >5-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

M vs. L: Medium current dioxin category versus low current dioxin category.

H vs. L: High current dioxin category versus low current dioxin category.

TABLE 15-12. (Continued)

**Analysis of FSH
(Discrete)**

Ranch Hands - Current Dioxin (Categorized) and Time - Adjusted					
Assumption	Time (Yrs.)	Current Dioxin Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
g) Minimal (n=521)	≤18.6	C-by-Ta		0.710	AGE (p=0.012)
		Overall†		0.583	
		M vs. L ^b	--	--	
		H vs. L ^b	--	--	
		M vs. L ^c	0.73 (0.30,1.78)	0.487 ^d	
		H vs. L ^c	0.52 (0.14,1.96)	0.332 ^d	
	>18.6	Overall†		0.768	
		M vs. L ^b	--	--	
		H vs. L ^b	--	--	
		M vs. L ^c	1.61 (0.65,4.02)	0.303 ^d	
h) Maximal (n=742)	≤18.6	C-by-Ta		0.047	AGE (p<0.001)
		Overall†		0.773	
		M vs. L ^b	0.97 (0.22,4.29)	0.973 ^d	
		H vs. L ^b	1.21 (0.23,6.54)	0.821 ^d	
		M vs. L ^c	0.61 (0.30,1.23)	0.167 ^d	
		H vs. L ^c	0.45 (0.13,1.49)	0.190 ^d	
	>18.6	Overall†		0.176	
		M vs. L ^b	0.95 (0.14,6.41)	0.957 ^d	
		H vs. L ^b	0.67 (0.07,6.62)	0.733 ^d	
		M vs. L ^c	2.43 (1.16,5.06)	0.018 ^d	
		H vs. L ^c	2.10 (0.87,5.09)	0.099 ^d	

^aTest of significance of current dioxin-by-time interaction.

^bLow FSH contrasted with normal FSH.

^cHigh FSH contrasted with normal FSH.

^dTest of significance for relative risk equal to 1 (current dioxin and time categorized).

†Overall test of independence of current dioxin and FSH within time stratum.

--: Adjusted relative risk, confidence interval, and 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: >5-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

M vs. L: Medium current dioxin category versus low current dioxin category.

H vs. L: High current dioxin category versus low current dioxin category.

TABLE 15-12. (Continued)

Analysis of FSH
(Discrete)

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

Current Dioxin Category	n	Percent			Contrast	Low versus Normal		High versus Normal	
		Low	Normal	High		Est. Relative Risk (95% C.I.)	p-Value	Est. Relative Risk (95% C.I.)	p-Value
Background	786	1.9	87.9	10.2					
Unknown	345	2.0	85.8	12.2	Unknown vs. Background	1.10 (0.45,2.70)	0.840	1.23 (0.82,1.83)	0.319
Low	196	2.0	84.7	13.3	Low vs. Background	1.13 (0.37,3.41)	0.829	1.36 (0.84,2.18)	0.210
High	187	2.1	87.2	10.7	High vs. Background	1.15 (0.38,3.48)	0.803	1.06 (0.63,1.79)	0.821
Total	1,514								All categories: p=0.912

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

Current Dioxin Category	n	Contrast	Low versus Normal		High versus Normal		Covariate Remarks
			Adj. Relative Risk (95% C.I.)	p-Value	Adj. Relative Risk (95% C.I.)	p-Value	
Background	786						AGE (p<0.001)
Unknown	345	Unknown vs. Background	1.20 (0.49,2.96)	0.691	1.14 (0.77,1.71)	0.508	
Low	196	Low vs. Background	1.14 (0.38,3.40)	0.821	1.38 (0.85,2.22)	0.190	
High	187	High vs. Background	0.93 (0.31,2.79)	0.895	1.41 (0.82,2.40)	0.212	
Total	1,514						All categories: p=0.826

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.

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Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted and adjusted analyses of categorized current dioxin were not significant for discretized FSH (Table 15-12 [i] and [j]: $p > 0.15$ for the overall current dioxin effect and all contrasts).

Testosterone (Continuous)

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

Treating testosterone as a continuous variable, a decreasing association with initial dioxin was observed in both the unadjusted minimal and maximal analyses, although the relationship was not significant (Table 15-13 [a] and [b]: $p = 0.679$ and $p = 0.126$, respectively).

The adjusted analyses revealed a significant initial dioxin-by-personality type interaction under both the minimal and maximal assumptions (Table 15-13 [c] and [d]: $p = 0.007$ and $p = 0.002$). Appendix Table N-1 presents stratified results. In each cohort, testosterone decreased significantly with initial dioxin for type A participants (minimal: $p = 0.006$; maximal: $p = 0.004$). In the minimal cohort, adjusted mean testosterone levels for type A participants decreased by 12.2 percent between the low and high initial dioxin categories (538.3, 514.8, and 472.1 ng/dl for the low, medium, and high initial dioxin categories); correspondingly, adjusted testosterone means for type A participants dropped by 10.6 percent between the low and high initial dioxin categories in the maximal cohort (562.4, 551.1, and 502.7 ng/dl for the low, medium, and high initial dioxin categories). In contrast, a nonsignificant positive association was seen between testosterone and initial dioxin for type B individuals in both cohorts.

Further analyses deleted the initial dioxin-by-personality type interaction. Because percent body fat was significantly associated with initial dioxin (see Chapter 6), the association between initial dioxin and testosterone was evaluated in the context of two models. Adjusting for age and percent body fat under the minimal assumption, and for age, race, and percent body fat for the maximal assumption, the association between initial dioxin and testosterone was not significant (Table 15-13 [c] and [d]: $p = 0.329$, minimal; $p = 0.237$, maximal). However, a significant negative association was seen for both cohorts when the percent body fat effect was excluded from the model (Appendix Table N-2: $p = 0.023$ for the minimal cohort and $p < 0.001$ for the maximal cohort). The adjusted mean testosterone levels were 559.9, 544.3, and 508.5 ng/dl for the low, medium, and high initial dioxin categories of the maximal cohort.

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the association between current dioxin and testosterone did not differ significantly between time since tour strata in either the unadjusted or adjusted analyses (Table 15-13 [e-h]: $p > 0.40$ for each analysis). The association between current dioxin and testosterone was also not significant in each of the individual time strata, either unadjusted or adjusted for age and percent body fat.

However, when percent body fat was excluded from the model, the association between current dioxin and testosterone was significantly negative for Ranch Hands with a later tour

TABLE 15-13.

**Analysis of Testosterone (ng/dl)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean ^a	Slope (Std. Error) ^b	p-Value
a) Minimal (n=516) (R ² <0.001)	Low	128	513.8	-0.0527 (0.1270)	0.679
	Medium	257	523.3		
	High	131	507.5		
b) Maximal (n=736) (R ² =0.003)	Low	184	538.7	-0.1436 (0.0937)	0.126
	Medium	366	519.4		
	High	186	511.8		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean ^a	Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
c) Minimal (n=501) (R ² =0.260)	Low	124	522.8***	-0.1127 (0.1155)***	0.329***	INIT*PERS (p=0.007) AGE (p<0.001) %BFAT (p<0.001)
	Medium	250	520.1***			
	High	127	505.1***			
d) Maximal (n=711) (R ² =0.239)	Low	175	542.9***	-0.1027 (0.0868)***	0.237***	INIT*PERS (p=0.002) AGE (p<0.001) RACE (p=0.055) %BFAT (p<0.001)
	Medium	356	543.0***			
	High	180	522.5***			

^aTransformed from square root scale.

^bSlope and standard error based on square root testosterone versus log₂ dioxin.

***Log₂ (initial dioxin)-by-covariate interaction (p≤0.01); 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: Log₂ (initial dioxin).

TABLE 15-13. (Continued)
Analysis of Testosterone (ng/dl)
(Continuous)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Mean ^a /(n) Current Dioxin			Slope (Std. Error) ^b	p-Value
		Low	Medium	High		
e) Minimal (n=516) (R ² =0.010)	≤18.6	521.9 (71)	545.2 (127)	517.8 (54)	-0.0063 (0.2062)	0.669 ^c 0.976 ^d
	>18.6	496.3 (57)	503.8 (130)	503.5 (77)		0.1077 (0.1687)
f) Maximal (n=736) (R ² =0.011)	≤18.6	555.4 (105)	532.5 (189)	528.7 (83)	-0.1240 (0.1453)	0.509 ^c 0.394 ^d
	>18.6	509.0 (79)	505.6 (176)	504.2 (104)		0.0042 (0.1282)

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean ^a /(n) Current Dioxin			Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=516) (R ² =0.243)	≤18.6	526.3 (71)	531.9 (127)	495.1 (54)	-0.1935 (0.1869)	0.410 ^c 0.301 ^d	AGE (p<0.001) %BFAT (p<0.001)
	>18.6	517.3 (57)	509.9 (130)	511.0 (77)			
h) Maximal (n=736) (R ² =0.224)	≤18.6	550.5 (105)	545.5 (189)	527.6 (83)	-0.1147 (0.1336)	0.690 ^c 0.391 ^d	AGE (p<0.001) RACE (p=0.126) %BFAT (p<0.001)
	>18.6	539.8 (79)	536.2 (176)	526.3 (104)			

^aTransformed from square root scale.

^bSlope and standard error based on square root testosterone versus log₂ dioxin.

^cTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^dTest of significance for slope equal to 0 (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 15-13. (Continued)
Analysis of Testosterone (ng/dl)
(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	785	525.3	All Categories		0.016
Unknown	343	554.2	Unknown vs. Background	28.9 --	0.005
Low	193	525.6	Low vs. Background	0.3 --	0.977
High	187	515.0	High vs. Background	-10.3 --	0.422
Total	1,508		(R ² =0.007)		

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	785	519.0	All Categories		0.248	%BFAT (p<0.001) AGE*RACE
Unknown	343	531.4	Unknown vs. Background	12.4 --	0.180	(p=0.041)
Low	193	521.6	Low vs. Background	2.6 --	0.821	
High	187	505.1	High vs. Background	-13.9 --	0.230	
Total	1,508		(R ² =0.203)			

^aTransformed from square root scale.

^eDifference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on square root scale.

^fp-value is based on difference of means on square root 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.

and marginally negative for Ranch Hands with an early tour under the maximal assumption (Appendix Table N-2: $p=0.012$ for $\text{time} \leq 18.6$ years and $p=0.069$ and $\text{time} > 18.6$ years). This demonstrates the percent body fat-dioxin effect seen in Chapter 6. The current dioxin-by-time interaction remained nonsignificant for both assumptions.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The mean testosterone differed significantly among the four current dioxin categories in the unadjusted analysis (Table 15-13 [i]: $p=0.016$). Of the three Ranch Hand versus background contrasts, the only significant finding was that the mean for the unknown category was significantly more than the background mean ($p=0.005$). The mean levels of testosterone were 525.3, 554.2, 525.6, and 515.0 ng/dl for the background, unknown, low, and high current dioxin categories.

After adjustment for percent body fat and the age-by-race interaction, no significant findings were noted (Table 15-13 [j]: $p > 0.15$ for all contrasts). However, the overall contrast became significant when percent body fat was deleted from the model (Appendix Table N-2: $p < 0.001$). For this analysis, the adjusted mean for the unknown current dioxin category was significantly more than the background mean ($p=0.001$) and the adjusted mean for the high current dioxin category was significantly less than the background mean ($p=0.010$). The adjusted means were 514.0, 545.9, 513.3, and 482.9 ng/dl for the background, unknown, low, and high current dioxin categories.

Testosterone (Discrete)

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

The prevalence of abnormally low testosterone levels was not significantly associated with initial dioxin in both the unadjusted minimal and maximal analyses (Table 15-14 [a] and [b]: $p=0.589$ and $p=0.581$).

These findings did not change after adjusting for age and percent body fat (Table 15-14 [c] and [d]: minimal, $p=0.568$; maximal, $p=0.846$).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the current dioxin-by-time since tour interaction was not significant in either the unadjusted or adjusted analyses (Table 15-14 [e-h]: $p > 0.40$ for each analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of abnormally low testosterone levels did not differ significantly among current dioxin categories in the unadjusted analysis of categorized current dioxin (Table 15-14 [i]: $p=0.649$). However, relatively more abnormally low values were found in the high current dioxin category than in the other categories (1.7%, 0.9%, 1.6%, and 2.1% for the background, unknown, low, and high current dioxin categories).

The adjusted analysis found a significant categorized current dioxin-by-personality type interaction (Table 15-14 [j]: $p=0.028$). For type A participants, the overall current dioxin

TABLE 15-14.
Analysis of Testosterone
(Discrete)

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal Low	Est. Relative Risk (95% C.I.)^a	p-Value
a) Minimal (n=516)	Low	128	3.1	0.88 (0.54,1.43)	0.589
	Medium	257	1.9		
	High	131	3.1		
b) Maximal (n=736)	Low	184	0.0	1.10 (0.78,1.56)	0.581
	Medium	366	3.3		
	High	186	2.2		
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted					
Assumption			Adj. Relative Risk (95% C.I.)^a	p-Value	Covariate Remarks
c) Minimal (n=516)			0.87 (0.53,1.43)	0.568	AGE (p=0.044) %BFAT (p<0.001)
d) Maximal (n=736)			1.04 (0.71,1.52)	0.846	AGE (p=0.010) %BFAT (p<0.001)

^aRelative 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 15-14. (Continued)

**Analysis of Testosterone
(Discrete)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal Low/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=516)	≤18.6	1.4 (71)	1.6 (127)	1.9 (54)	0.75 (0.26,2.18)	0.983 ^b 0.600 ^c
	>18.6	7.0 (57)	1.5 (130)	3.9 (77)	0.74 (0.40,1.38)	0.347 ^c
f) Maximal (n=736)	≤18.6	0.0 (105)	1.6 (189)	1.2 (83)	1.22 (0.59,2.55)	0.444 ^b 0.592 ^c
	>18.6	2.5 (79)	4.0 (176)	2.9 (104)	0.87 (0.56,1.34)	0.528 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
g) Minimal (n=516)	≤18.6	0.53 (0.17,1.69)	0.796 ^b 0.285 ^c	%BFAT (p<0.001)
	>18.6	0.63 (0.33,1.19)	0.154 ^c	
h) Maximal (n=736)	≤18.6	1.00 (0.44,2.25)	0.762 ^b 0.992 ^c	AGE (p=0.045) %BFAT (p<0.001)
	>18.6	0.86 (0.54,1.37)	0.536 ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest 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 15-14. (Continued)

**Analysis of Testosterone
(Discrete)**

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

Current Dioxin Category	n	Percent Abnormal Low	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	785	1.7	All Categories		0.649
Unknown	343	0.9	Unknown vs. Background	0.52 (0.15,1.85)	0.315
Low	193	1.6	Low vs. Background	0.94 (0.26,3.32)	0.921
High	187	2.1	High vs. Background	1.30 (0.42,4.03)	0.652
Total	1,508				

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	750	All Categories		0.899**	DXCAT*PERS (p=0.028)
Unknown	326	Unknown vs. Background	0.72 (0.20,2.58)**	0.610**	AGE (p=0.020)
Low	189	Low vs. Background	0.89 (0.24,3.21)**	0.854**	RACE (p=0.109)
High	181	High vs. Background	1.30 (0.39,4.31)**	0.667**	%BFAT (p<0.001)
Total	1,446				

**Categorized current dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤ 10 ppt.
 Unknown (Ranch Hands): Current Dioxin ≤ 10 ppt.
 Low (Ranch Hands): $15 \text{ ppt} < \text{Current Dioxin} \leq 33.3 \text{ ppt}$.
 High (Ranch Hands): Current Dioxin $> 33.3 \text{ ppt}$.

effect was marginally significant (Appendix Table N-1: $p=0.096$) and the relative risk of abnormally low testosterone levels for the high versus background contrast was significant (Adj. RR=6.72, 95% C.I.: [1.06,42.73], $p=0.044$). The results for type B individuals did not show a significant difference among current dioxin categories ($p>0.25$ for all contrasts).

The interaction was then excluded from the model. After adjusting for age, race, and percent body fat, no significant difference was found among current dioxin categories (Table 15-14 [j]: $p=0.899$).

Fasting Glucose (Continuous)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

Under both the minimal and maximal assumptions, the unadjusted initial dioxin analyses found a significant association with fasting glucose in its continuous form (Table 15-15 [a] and [b]: $p=0.027$ and $p<0.001$, respectively). The mean levels of fasting glucose were 102.4, 103.1, and 102.2 mg/dl for the low, medium, and high initial dioxin categories under the minimal assumption. The corresponding means under the maximal assumption were 99.4, 101.6, and 104.6 mg/dl.

The adjusted analyses under both assumptions found a highly significant positive association between initial dioxin and fasting glucose (Table 15-15 [c] and [d]: $p<0.001$ for both the minimal and maximal assumptions). The adjusted means increased with initial dioxin (minimal: 104.1, 105.6, and 106.8 mg/dl; maximal: 103.5, 104.7, and 110.4 mg/dl for the low, medium, and high initial dioxin categories).

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

The unadjusted current dioxin and time since tour analysis for fasting glucose in its continuous form found that the interaction between current dioxin and time was marginally significant under the minimal assumption (Table 15-15 [e]: $p=0.096$), but it was not significant under the maximal assumption (Table 15-15 [f]: $p=0.242$). For both cohorts, the association between current dioxin and fasting glucose was significantly positive for Ranch Hands with an early tour (time>18.6: slope=0.0251, $p=0.009$ for the minimal cohort; slope=0.0205, $p=0.002$ for the maximal cohort). The mean levels of fasting glucose for the low, medium, and high current dioxin categories in this time stratum were 102.6, 102.9, and 105.7 mg/dl for the minimal cohort, and 99.8, 102.5, and 106.0 mg/dl for the maximal cohort. The association between current dioxin and fasting glucose was not significant for Ranch Hands with an early tour ($p=0.993$ and $p=0.241$ for the minimal and maximal cohorts).

The adjusted minimal analysis displayed findings similar to the unadjusted analysis. The current dioxin-by-time interaction was of borderline significance (Table 15-15 [g]: $p=0.097$). A significant association between current dioxin and fasting glucose was seen for Ranch Hands with an early tour (time>18.6: Adj. slope=0.0393, $p<0.001$), but the association was not significant for Ranch Hands with a later tour (time≤18.6: Adj. slope=0.0149, $p=0.209$). The adjusted mean levels of fasting glucose for Ranch Hands with an early tour were 102.4, 104.5, and 109.7 mg/dl for the low, medium, and high current dioxin categories.

TABLE 15-15.

**Analysis of Fasting Glucose (mg/dl)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean ^a	Slope (Std. Error) ^b	p-Value
a) Minimal (n=517) (R ² =0.010)	Low	130	102.4	0.0160 (0.0072)	0.027
	Medium	257	103.1		
	High	130	102.2		
b) Maximal (n=737) (R ² =0.016)	Low	184	99.4	0.0168 (0.0048)	<0.001
	Medium	368	101.6		
	High	185	104.6		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean ^a	Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
c) Minimal (n=511) (R ² =0.095)	Low	130	104.1	0.0262 (0.0073)	<0.001	AGE (p<0.001) RACE*ALC (p=0.021) RACE*DRKYR (p=0.002)
	Medium	253	105.6			
	High	128	106.8			
d) Maximal (n=728) (R ² =0.106)	Low	182	103.5	0.0216 (0.0048)	<0.001	AGE*RACE (p=0.005) AGE*DRKYR (p=0.018) RACE*DRKYR (p=0.034)
	Medium	365	104.7			
	High	181	110.4			

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm fasting glucose versus log₂ 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 15-15. (Continued)
Analysis of Fasting Glucose (mg/dl)
(Continuous)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean ^a /(n) Current Dioxin			Slope (Std. Error) ^b	p-Value	
		Low	Medium	High			
e) Minimal (n=517) (R ² =0.015)	≤18.6	101.3 (72)	103.5 (126)	98.4 (53)	-0.0001 (0.0117)	0.096 ^c 0.993 ^d	
	>18.6	102.6 (58)	102.9 (131)	105.7 (77)	0.0251 (0.0096)	0.009 ^d	
f) Maximal (n=737) (R ² =0.018)	≤18.6	98.2 (105)	100.7 (189)	104.0 (82)	0.0088 (0.0075)	0.242 ^c 0.241 ^d	
	>18.6	99.8 (79)	102.5 (178)	106.0 (104)	0.0205 (0.0066)	0.002 ^d	

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean ^a /(n) Current Dioxin			Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=511) (R ² =0.103)	≤18.6	103.4 (72)	107.4 (125)	104.5 (52)	0.0149 (0.0118)	0.097 ^c 0.209 ^d	AGE*RACE (p=0.019) RACE*DRKYR (p=0.043)
	>18.6	102.4 (58)	104.5 (128)	109.7 (76)	0.0393 (0.0096)	<0.001 ^d	
h) Maximal (n=728) (R ² =0.122)	≤18.6	102.3** (104)	104.9** (188)	110.8** (80)	0.0168 (0.0075)**	0.194*** 0.024*** ^d	CURR*TIME*AGE (p=0.041) AGE*RACE (p=0.004) AGE*DRKYR (p=0.015) RACE*DRKYR (p=0.030)
	>18.6	101.7** (78)	104.5** (176)	111.1** (102)	0.0294 (0.0066)**	<0.001*** ^d	

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm fasting glucose versus log₂ dioxin.

^cTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^dTest of significance for slope different from 0 (current dioxin continuous, time categorized).

**Log₂ (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

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 15-15. (Continued)
Analysis of Fasting Glucose (mg/dl)
(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	99.5	All Categories		<0.001
Unknown	341	98.3	Unknown vs. Background	-1.2 --	0.206
Low	193	100.7	Low vs. Background	1.2 --	0.331
High	186	105.1	High vs. Background	5.6 --	<0.001
Total	1,499		(R ² =0.017)		

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	777	101.3***	All Categories		<0.001***	DXCAT*AGE (p<0.001)
Unknown	338	99.9***	Unknown vs. Background	-1.4 -- ***	0.151***	DXCAT*DRKYR (p=0.044)
Low	191	102.7***	Low vs. Background	1.4 -- ***	0.250***	
High	182	108.9***	High vs. Background	7.6 -- ***	<0.001***	AGE*RACE (p=0.018)
Total	1,488		(R ² =0.101)			AGE*DRKYR (p=0.046)

^aTransformed from natural logarithm scale.

^eDifference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

^fp-value is based on difference of means on natural logarithm scale.

***Categorized current dioxin-by-covariate interaction (p≤0.01); adjusted mean and p-value derived from a model fitted after deletion of this interaction.

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 adjusted maximal analysis detected a significant current dioxin-by-time-by-age interaction (Table 15-15 [h]: $p=0.041$). Stratified analyses found a significant interaction between current dioxin and time for younger Ranch Hands, those born in or after 1942 (Appendix Table N-1: $p=0.031$). The association between current dioxin and fasting glucose was significant for younger Ranch Hands with an early tour (time >18.6 : Adj. slope= 0.0319 , $p=0.002$), but it was not significant for those with a later tour (time ≤ 18.6 : Adj. slope= 0.0017 , $p=0.854$). The adjusted mean levels of fasting glucose for the early time stratum were 94.3, 95.3, and 100.1 mg/dl for the low, medium, and high current dioxin categories.

The interaction between current dioxin and time was not significant for older Ranch Hands (born <1942 : $p=0.451$), but the association between current dioxin and fasting glucose was significant within each time stratum (time ≤ 18.6 : Adj. slope= 0.0370 , $p=0.003$; time >18.6 : Adj. slope= 0.0254 , $p=0.006$). The adjusted mean levels of fasting glucose increased for the low, medium, and high current dioxin categories for both time strata (time ≤ 18.6 : 103.4, 109.1, and 122.8 mg/dl; time >18.6 : 105.1, 109.0, and 114.8 mg/dl).

Ignoring the current dioxin-by-time-by-age interaction, the adjusted maximal analysis did not find a significant interaction between current dioxin and time (Table 15-15 [h]: $p=0.194$). However, the association between current dioxin and fasting glucose was significant within each time stratum (time ≤ 18.6 : Adj. slope= 0.0168 , $p=0.024$; time >18.6 : Adj. slope= 0.0294 , $p<0.001$). The adjusted mean levels of fasting glucose increased with current dioxin for both time strata (time ≤ 18.6 : 102.3, 104.9, and 110.8 mg/dl; time >18.6 : 101.7, 104.5, and 111.1 mg/dl for the low, medium, and high current dioxin categories).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of categorized current dioxin found that the mean levels of fasting glucose differed significantly among current dioxin categories (Table 15-15 [i]: 99.5, 98.3, 100.7, and 105.1 mg/dl for the background, unknown, low, and high current dioxin categories, $p<0.001$). The mean for the high current dioxin category was significantly more than the background mean ($p<0.001$). The means for the unknown and low categories did not differ significantly from the background mean ($p=0.206$ and $p=0.331$, respectively).

The adjusted analysis detected two significant categorized current dioxin-by-covariate interactions—categorized current dioxin-by-age (Table 15-15 [j]: $p<0.001$) and categorized current dioxin-by-lifetime alcohol history ($p=0.044$). Age and lifetime alcohol history were categorized to explore these interactions. Separate analyses were done for younger Ranch Hands (born ≥ 1942) and older Ranch Hands (born <1942). The categorized current dioxin-by-lifetime alcohol history interaction was not significant for younger Ranch Hands ($p=0.807$), but it was significant for older Ranch Hands ($p=0.050$). The mean level of fasting glucose differed significantly among current dioxin categories for younger Ranch Hands (Appendix Table N-1: 96.1, 95.5, 96.5, and 100.0 mg/dl for the background, unknown, low, and high current dioxin categories, $p=0.017$), with the mean for the high current dioxin category being significantly more than the background mean ($p=0.004$).

Appendix Table N-1 presents results stratified by lifetime alcohol history for older Ranch Hands because of the significant interaction. They show that the overall contrast was

not significant for older Ranch Hands who never had drunk ($p=0.567$), but that the overall difference among adjusted mean levels of fasting glucose was significant for older Ranch Hands who were moderate lifetime drinkers ($>0-40$: 102.5, 100.7, 106.1, and 112.2 mg/dl for the background, unknown, low, and high current dioxin categories, $p=0.003$) and for those who were heavy lifetime drinkers (>40 : 107.2, 105.4, 105.8, and 127.4 mg/dl for the background, unknown, low, and high current dioxin categories, $p<0.001$). The low versus background contrast was marginally significant for older Ranch Hands who were moderate drinkers ($p=0.091$). The high versus background contrast was significant for older Ranch Hands who were moderate drinkers ($p=0.004$) and for those who were heavy drinkers ($p<0.001$). For older Ranch Hands, the difference in adjusted means for the high versus background contrast increased with lifetime alcohol consumption (0: 7.1 mg/dl; $>0-40$: 9.7 mg/dl; >40 : 20.2 mg/dl).

The adjusted results paralleled the unadjusted findings after deleting the interactions. The overall contrast was highly significant (Table 15-15 [j]: $p<0.001$), as was the high versus background contrast ($p<0.001$). The adjusted means for the background, unknown, low, and high current dioxin categories were 101.3, 99.9, 102.7, and 108.9 mg/dl.

Fasting Glucose (Discrete)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

The unadjusted initial dioxin analyses of discretized fasting glucose detected a significant relative risk of an abnormally high level of fasting glucose for each cohort (Table 15-16 [a]: Est. RR=1.25, $p=0.022$ for the minimal cohort; Table 15-16 [b]: Est. RR=1.29, $p<0.001$ for the maximal cohort). For the minimal cohort, the percentages of abnormal fasting glucose levels were 15.4, 14.8, and 17.7 percent for the low, medium, and high initial dioxin categories. The corresponding percentages for the maximal cohort were 8.2, 13.9, and 19.5 percent.

The adjusted analyses displayed a highly significant increased risk of an abnormally high level of fasting glucose for both cohorts (Table 15-16 [c] and [d]: $p<0.001$ for both analyses). Adjusting for age, the relative risk of an abnormally high level of fasting glucose was 1.45 for the minimal cohort. The relative risk was 1.48 for the maximal cohort, adjusting for age and race.

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not significant in either the unadjusted minimal (Table 15-16 [e]: $p=0.256$) or maximal (Table 15-16 [f]: $p=0.531$) analysis of discretized fasting glucose. Under both assumptions, the estimated relative risk was significantly greater than 1 for Ranch Hands with an early tour (Est. RR=1.32, $p=0.023$ for the minimal cohort; Est. RR=1.30, $p=0.006$ for the maximal cohort).

In the adjusted minimal analysis, the current dioxin-by-time interaction remained nonsignificant (Table 15-16 [g]: $p=0.396$) and the relative risk of an abnormally high level of fasting glucose remained significant for Ranch Hands with an early tour (Adj. RR=1.59, $p<0.001$). However, the adjusted maximal analysis detected a significant current dioxin-by-time-by-race interaction (Table 15-16 [h]: $p=0.038$). Appendix Table N-1 presents

TABLE 15-16.
Analysis of Fasting Glucose
(Discrete)

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.) ^a	p-Value
a) Minimal (n=517)	Low	130	15.4	1.25 (1.03,1.50)	0.022
	Medium	257	14.8		
	High	130	17.7		
b) Maximal (n=737)	Low	184	8.2	1.29 (1.12,1.49)	<0.001
	Medium	368	13.9		
	High	185	19.5		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
c) Minimal (n=517)	1.45 (1.18,1.77)	<0.001	AGE (p<0.001)
d) Maximal (n=737)	1.48 (1.26,1.74)	<0.001	AGE (p<0.001) RACE (p=0.100)

^aRelative 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 15-16. (Continued)
Analysis of Fasting Glucose
(Discrete)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	13.9 (72)	14.3 (126)	11.3 (53)	1.04 (0.74,1.45)	0.256 ^b 0.821 ^c
	>18.6	13.8 (58)	16.0 (131)	23.4 (77)	1.32 (1.04,1.67)	0.023 ^c
f) Maximal (n=737)	≤18.6	5.7 (105)	12.7 (189)	17.1 (82)	1.18 (0.93,1.50)	0.531 ^b 0.183 ^c
	>18.6	11.4 (79)	14.6 (178)	22.1 (104)	1.30 (1.08,1.56)	0.006 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
g) Minimal (n=517)	≤18.6	1.33 (0.93,1.89)	0.396 ^b 0.118 ^c	AGE (p<0.001)
	>18.6	1.59 (1.23,2.05)	<0.001 ^c	
h) Maximal (n=728)	≤18.6	1.44 (1.10,1.88)**	0.666** ^b 0.007** ^c	CURR*TIME*RACE (p=0.038) DRKYR (p=0.122) AGE*RACE (p=0.040)
	>18.6	1.55 (1.26,1.91)**	<0.001** ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log₂ (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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 15-16. (Continued)
Analysis of Fasting Glucose
(Discrete)

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

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	11.4	All Categories		0.001
Unknown	341	7.9	Unknown vs. Background	0.67 (0.42,1.05)	0.078
Low	193	12.4	Low vs. Background	1.10 (0.68,1.78)	0.695
High	186	19.9	High vs. Background	1.93 (1.26,2.94)	0.002
Total	1,499				

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		<0.001	AGE (p<0.001) RACE (p=0.042) DRKYR (p=0.033)
Unknown	338	Unknown vs. Background	0.66 (0.42,1.05)	0.081	
Low	191	Low vs. Background	1.18 (0.72,1.94)	0.510	
High	182	High vs. Background	2.95 (1.87,4.66)	<0.001	
Total	1,488				

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

stratified results that show sparse data for Blacks. The current dioxin-by-time interaction was not significant for non-Blacks ($p=0.477$), but the relative risk of an abnormally high level of fasting glucose was significantly more than 1 in each time stratum (time \leq 18.6: Adj. RR=1.39, $p=0.015$; time $>$ 18.6: Adj. RR=1.57, $p<0.001$). After excluding the current dioxin-by-time-by-race interaction, the adjusted maximal results were comparable to the stratified findings for non-Blacks. The current dioxin-by-time interaction was not significant (Table 15-16 [h]: $p=0.666$), but the association between current dioxin and fasting glucose was significant within both time strata (time \leq 18.6: Adj. RR=1.44, $p=0.007$; time $>$ 18.6: Adj. RR=1.55, $p<0.001$).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis found that the prevalence of abnormally high levels of fasting glucose differed significantly among the current dioxin categories (Table 15-16 [i]: 11.4%, 7.9%, 12.4%, and 19.9% for the background, unknown, low, and high current dioxin categories, $p=0.001$). The estimated relative risk for the unknown versus background contrast was marginally less than 1 (Est. RR=0.67, 95% C.I.: [0.42,1.05], $p=0.078$), and it was significantly more than 1 for the high versus background contrast (Est. RR=1.93, 95% C.I.: [1.26,2.94], $p=0.002$).

Adjusting for age, race, and lifetime alcohol history, the overall contrast remained highly significant (Table 15-16 [j]: $p<0.001$), with the unknown versus background contrast essentially unchanged (Adj. RR=0.66, 95% C.I.: [0.42,1.05], $p=0.081$). However, the adjusted relative risk for the high versus background contrast increased more than 50 percent to 2.95 (95% C.I.: [1.87,4.66], $p<0.001$).

2-Hour Postprandial Glucose (Continuous)

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

Under the minimal assumption, the association between initial dioxin and 2-hour postprandial glucose was not significant in the unadjusted analysis (Table 15-17 [a]: $p=0.177$). However, the unadjusted maximal analysis detected a significant positive association (Table 15-17 [b]: $p=0.021$). The unadjusted mean postprandial glucose levels for the maximal cohort were 108.0, 112.1, and 114.0 mg/dl for the low, medium, and high initial dioxin categories.

The adjusted minimal analysis revealed a significant initial dioxin-by-percent body fat interaction (Table 15-17 [c]: $p=0.045$). Percent body fat was categorized to explore the interaction. Stratified analyses showed that a positive association between initial dioxin and 2-hour postprandial glucose was stronger for obese Ranch Hands than for normal/lean Ranch Hands, but neither finding was significant (Appendix Table N-1).

The interaction between initial dioxin and percent body fat was then removed from the model. Adjusting for age and percent body fat, the relationship between initial dioxin and 2-hour postprandial glucose was not significant (Table 15-17 [c]: $p=0.114$). However, similar to the testosterone findings, the association became significant when percent body fat was excluded from the model (Appendix Table N-2: $p=0.020$).

TABLE 15-17.

**Analysis of 2-Hour Postprandial Glucose (mg/dl)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted						
Assumption	Initial Dioxin	n	Mean ^a	Slope (Std. Error) ^b	p-Value	
a) Minimal (n=467) (R ² =0.004)	Low	117	112.3	0.0146 (0.0108)	0.177	
	Medium	231	112.9			
	High	119	113.8			
b) Maximal (n=678) (R ² =0.008)	Low	177	108.0	0.0178 (0.0077)	0.021	
	Medium	337	112.1			
	High	164	114.0			

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean ^a	Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
c) Minimal (n=467) (R ² =0.111)	Low	117	111.9**	0.0169 (0.0107)**	0.114**	INIT*%BFAT (p=0.045) AGE (p<0.001)
	Medium	231	113.6**			
	High	119	113.6**			
d) Maximal (n=654) (R ² =0.105)	Low	168	110.2	0.0118 (0.0079)	0.135	AGE (p<0.001) PERS (p=0.127) %BFAT (p<0.001)
	Medium	328	111.6			
	High	158	113.4			

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm 2-hour postprandial glucose versus log₂ dioxin.

**Log₂ (initial dioxin)-by-covariate interaction (0.01<p≤0.05); 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.

TABLE 15-17. (Continued)

**Analysis of 2-Hour Postprandial Glucose (mg/dl)
(Continuous)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Mean ^a /(n) Current Dioxin			Slope (Std. Error) ^b	p-Value
		Low	Medium	High		
e) Minimal (n=467) (R ² =0.014)	≤18.6	107.3 (63)	110.2 (117)	110.5 (51)	0.0137 (0.0170)	0.555 ^c 0.421 ^d
	>18.6	126.7 (52)	110.5 (116)	119.3 (68)	0.0005 (0.0145)	0.975 ^d
f) Maximal (n=678) (R ² =0.010)	≤18.6	109.3 (105)	109.0 (174)	111.3 (74)	0.0073 (0.0116)	0.406 ^c 0.530 ^d
	>18.6	104.0 (74)	116.7 (159)	116.6 (92)	0.0204 (0.0107)	0.057 ^d

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Mean ^a /(n) Current Dioxin			Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=453) (R ² =0.112)	≤18.6	106.9** (60)	111.6** (114)	111.6** (48)	0.0188 (0.0168)**	0.486*** ^c 0.264*** ^d	CURR*TIME*PERS (p=0.038)
	>18.6	124.6** (51)	110.5** (113)	117.9** (67)	0.0039 (0.0143)**	0.785*** ^d	AGE (p=0.001) %BFAT (p<0.001)
h) Maximal (n=654) (R ² =0.107)	≤18.6	112.3 (98)	109.9 (168)	112.4 (70)	0.0012 (0.0120)	0.252 ^c 0.921 ^d	AGE (p<0.001) PERS (p=0.110)
	>18.6	103.1 (72)	115.5 (156)	114.3 (90)	0.0190 (0.0107)	0.077 ^d	%BFAT (p<0.001)

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm 2-hour postprandial glucose versus log₂ dioxin.

^cTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^dTest of significance for slope equal to 0 (current dioxin continuous, time categorized).

**Log₂ (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

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 15-17. (Continued)
Analysis of 2-Hour Postprandial Glucose (mg/dl)
(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	740	111.3	All Categories		0.082	
Unknown	331	107.5	Unknown vs. Background	-3.8 --	0.049	
Low	179	109.8	Low vs. Background	-1.5 --	0.527	
High	166	114.2	High vs. Background	2.9 --	0.263	
Total	1,416		(R ² =0.005)			

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	705	110.9	All Categories		0.557	AGE (p<0.001) %BFAT (p<0.001) PERS (p=0.076)
Unknown	314	109.5	Unknown vs. Background	-1.4 --	0.471	
Low	175	109.3	Low vs. Background	-1.6 --	0.507	
High	160	113.1	High vs. Background	2.2 --	0.380	
Total	1,354		(R ² =0.107)			

^aTransformed from natural logarithm scale.

^eDifference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

^fP-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.

The maximal analyses were comparable. Adjusting for age, percent body fat, and personality type, the association between initial dioxin and 2-hour postprandial glucose was not significant (Table 15-17 [d]: $p=0.135$). But when percent body fat was removed from the model, the association was highly significant (Appendix Table N-2: $p=0.003$). The adjusted mean postprandial glucose levels for the low, medium, and high initial dioxin categories were 108.0, 111.6, and 115.8 mg/dl.

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

In the unadjusted analyses, the current dioxin-by-time since tour interaction was not significant under either the minimal (Table 15-17 [e]: $p=0.555$) or maximal (Table 15-17 [f]: $p=0.406$) assumption. Under the maximal assumption, the association between current dioxin and 2-hour postprandial glucose was marginally positive for Ranch Hands with more than 18.6 years since exposure ($p=0.057$). For these participants, the mean postprandial glucose levels were 104.0, 116.7, and 116.6 mg/dl for low, medium, and high current dioxin.

The current dioxin-by-time-by-personality type interaction was significant for the adjusted minimal analysis (Table 15-17 [g]: $p=0.038$). Stratified results showed that the current dioxin-by-time interaction was marginally significant for type B participants (Appendix Table N-1: $p=0.074$), but not significant for type A participants ($p=0.221$). The association between current dioxin and 2-hour postprandial glucose was not significant for each time stratum. The three-way interaction can be partly explained by noting that the adjusted slopes for the corresponding time strata were in the opposite direction for type A participants versus type B participants.

Excluding the interaction and adjusting for age and percent body fat, the current dioxin-by-time interaction was not significant for the minimal cohort (Table 15-17 [g]: $p=0.486$).

The results for the adjusted maximal analysis were consistent with the unadjusted findings. After adjusting for age, percent body fat, and personality type, the test of homogeneity of slopes was not significant (Table 15-17 [h]: $p=0.252$). However, a marginally significant association between current dioxin and 2-hour postprandial glucose ($p=0.077$) was found for Ranch Hands with an early tour of duty. This finding was significant when percent body fat was removed from the model (Appendix Table N-2: $p=0.009$).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The mean 2-hour postprandial glucose differed marginally among the four current dioxin categories in the unadjusted analysis (Table 15-17 [i]: $p=0.082$). The mean for the unknown category was significantly less than the background mean (107.5 mg/dl versus 111.3 mg/dl, $p=0.049$).

No significant results were found after adjusting for age, percent body fat, and personality type (Table 15-17 [j]: $p>0.35$ for all contrasts). However, the overall contrast became significant (Appendix Table N-2: $p=0.010$) when percent body fat was excluded from the model. The adjusted means were 111.1, 107.0, 110.1, and 116.5 mg/dl for the background, unknown, low, and high current dioxin categories. The adjusted mean for the high category was significantly more than the background mean ($p=0.041$), and the adjusted mean for the unknown category was significantly less than the background mean ($p=0.035$).

2-Hour Postprandial Glucose (Discrete)

Model 1: Ranch Hands – Initial Dioxin (Categorized)

The unadjusted analyses of discretized 2-hour postprandial glucose did not detect an overall association with initial dioxin for either the minimal ($p=0.174$) or maximal ($p=0.243$) cohorts (Table 15-18 [a] and [b]). However, the high versus low initial dioxin category contrast showed a marginally significant risk of diabetic glucose levels for both cohorts (minimal: Est. RR=7.00, 95% C.I.: [0.85,58.00], $p=0.071$; maximal: Est. RR=2.85, 95% C.I.: [0.97,8.33], $p=0.056$). The percentage of Ranch Hands with diabetic glucose levels increased for the low, medium, and high initial dioxin categories (0.9%, 2.6%, and 5.9% for the minimal cohort; 2.1%, 2.6%, and 5.9% for the maximal cohort).

Adjusting for age and percent body fat, similar findings were noted. The overall association with initial dioxin was not significant (Table 15-18 [c] and [d]: $p=0.229$ and $p=0.237$ for the minimal and maximal assumptions), but the high versus low initial dioxin category contrast of diabetic glucose levels was marginally significant under each assumption (minimal: Adj. RR=5.95, 95% C.I.: [0.91,38.81], $p=0.062$; maximal: Adj. RR=2.98, 95% C.I.: [0.97,9.14], $p=0.057$).

Further adjusted analyses were done excluding percent body fat from the model. They found a marginally significant overall association with initial dioxin for the maximal cohort (Appendix Table N-2: $p=0.091$). The high versus low initial dioxin category contrast of diabetic glucose levels was significant for both cohorts (Adj. RR=7.99, 95% C.I.: [1.10,57.96], $p=0.040$ for the minimal cohort; Adj. RR=3.85, 95% C.I.: [1.28,11.57], $p=0.016$ for the maximal cohort).

Model 2: Ranch Hands – Current Dioxin (Categorized) and Time

The current dioxin-by-time since tour interaction was not significant for either the unadjusted minimal ($p=0.444$) or maximal ($p=0.781$) analysis of discretized 2-hour postprandial glucose (Table 15-18 [e] and [f]). However, for the minimal cohort, the medium versus low current dioxin category contrast for the risk of impaired glucose levels was significantly less than 1 for Ranch Hands with more than 18.6 years since exposure (Est. RR=0.44, 95% C.I.: [0.21,0.92], $p=0.029$) and the high versus low contrast was marginally less than 1 for this time stratum (Est. RR=0.47, 95% C.I.: [0.20,1.08], $p=0.074$). For Ranch Hands with time 18.6 years or less, the relative risk of diabetic glucose levels for the high versus low contrast was significant under the maximal assumption (Est. RR=5.02, 95% C.I.: [1.08,23.32], $p=0.039$). The percentages of diabetic glucose levels for this time stratum were 1.6, 1.7, and 7.8 percent for the low, medium, and high current dioxin categories.

Adjusting for age, race, and percent body fat, the current dioxin-by-time interaction remained nonsignificant for both assumptions (Table 15-18 [g] and [h]: $p=0.358$ and $p=0.813$ for the minimal and maximal assumptions). However, within each time stratum, particular category contrasts were significant or marginally significant. For Ranch Hands with a later tour, the risk of diabetic glucose levels was greater for the high current dioxin category relative to the low current dioxin category (Adj. RR=5.20, 95% C.I.: [0.82,32.91], $p=0.080$ for the minimal cohort; Adj. RR=5.33, 95% C.I.: [1.22,23.28], $p=0.026$ for the maximal cohort). Also, similar to the unadjusted results for Ranch Hands with an early tour, the risk of impaired glucose levels was significantly less for the medium current dioxin category relative

TABLE 15-18.

**Analysis of 2-Hour Postprandial Glucose
(Discrete)**

Ranch Hands - Initial Dioxin (Categorized) - Unadjusted

Assumption	Initial Dioxin	n	Percent			Initial Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
			Normal	Impaired	Diabetic			
a) Minimal (n=467)	Low	117	81.2	17.9	0.9	Overall [†]		0.174
	Medium	231	78.4	19.0	2.6	M vs. L ^a	1.10 (0.62,1.96)	0.749
	High	119	79.8	14.3	5.9	H vs. L ^a	0.81 (0.40,1.63)	0.554
						M vs. L ^b	3.15 (0.37,26.54)	0.291
						H vs. L ^b	7.00 (0.85,58.00)	0.071
b) Maximal (n=678)	Low	326	82.8	15.0	2.1	Overall [†]		0.243
	Medium	233	78.5	18.9	2.6	M vs. L ^a	1.32 (0.85,2.07)	0.219
	High	119	79.8	14.3	5.9	H vs. L ^a	0.99 (0.54,1.80)	0.963
						M vs. L ^b	1.26 (0.42,3.82)	0.677
						H vs. L ^b	2.85 (0.97,8.33)	0.056

Ranch Hands - Initial Dioxin (Categorized) - Adjusted

Assumption	Initial Dioxin Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) Minimal (n=467)	Overall [†]		0.229	AGE (p=0.002)
	M vs. L ^a	1.17 (0.65,2.10)	0.609	%BFAT (p<0.001)
	H vs. L ^a	0.93 (0.45,1.93)	0.319	
	M vs. L ^b	2.57 (0.40,16.44)	0.845	
	H vs. L ^b	5.95 (0.91,38.81)	0.062	
d) Maximal (n=678)	Overall [†]		0.237	AGE (p<0.001)
	M vs. L ^a	1.39 (0.87,2.19)	0.164	%BFAT (p<0.001)
	H vs. L ^a	1.15 (0.61,2.15)	0.671	
	M vs. L ^b	1.28 (0.43,3.81)	0.657	
	H vs. L ^b	2.98 (0.97,9.14)	0.057	

^aImpaired contrasted with normal.

^bDiabetic contrasted with normal.

[†]Overall test of independence of initial dioxin and 2-hour postprandial glucose.

Note: **Minimal**--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

M vs. L: Medium initial dioxin category versus low initial dioxin category.

H vs. L: High initial dioxin category versus low initial dioxin category.

TABLE 15-18. (Continued)
Analysis of 2-Hour Postprandial Glucose
(Discrete)

Ranch Hands - Current Dioxin (Categorized) and Time - Unadjusted									
Assumption	Time (Yrs.)	Glucose Category	Percent/(n)			Current Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value	
			Current Dioxin						
			Low	Medium	High				
e) Minimal (n=467)	≤18.6	Normal	87.3	83.8	82.4	C-by-T ^a		0.444	
		Impaired	11.1	14.5	9.8	Overall [†]		0.297	
		Diabetic		1.6	1.7	7.8	M vs. L ^b	1.36 (0.53,3.49)	0.519 ^d
				(63)	(117)	(51)	H vs. L ^b	0.94 (0.28,3.16)	0.915 ^d
							M vs. L ^c	1.12 (0.10,12.66)	0.925 ^d
							H vs. L ^c	5.24 (0.56,48.61)	0.145 ^d
	>18.6	Normal	63.5	79.3	75.0	Overall [†]		0.105	
		Impaired	34.6	19.0	19.1	M vs. L ^b	0.44 (0.21,0.92)	0.029 ^d	
		Diabetic		1.9	1.7	5.9	H vs. L ^b	0.47 (0.20,1.08)	0.074 ^d
				(52)	(116)	(68)	M vs. L ^c	0.72 (0.06,8.18)	0.789 ^d
					H vs. L ^c	2.59 (0.28,24.18)	0.406 ^d		
f) Maximal (n=678)	≤18.6	Normal	85.4	83.8	82.4	C-by-T ^a		0.781	
		Impaired	13.0	14.5	9.8	Overall [†]		0.251	
		Diabetic		1.6	1.7	7.8	M vs. L ^b	1.14 (0.58,2.23)	0.700 ^d
				(185)	(117)	(51)	H vs. L ^b	0.78 (0.28,2.18)	0.641 ^d
							M vs. L ^c	1.07 (0.18,6.55)	0.938 ^d
							H vs. L ^c	5.02 (1.08,23.32)	0.039 ^d
	>18.6	Normal	75.9	79.3	75.0	Overall [†]		0.658	
		Impaired	20.6	19.0	19.1	M vs. L ^b	0.88 (0.47,1.64)	0.690 ^d	
		Diabetic		3.5	1.7	5.9	H vs. L ^b	0.94 (0.45,1.96)	0.866 ^d
				(141)	(116)	(68)	M vs. L ^c	0.46 (0.09,2.45)	0.365 ^d
					H vs. L ^c	1.68 (0.43,6.51)	0.456 ^d		

^aTest of significance of current dioxin-by-time interaction.

^bImpaired contrasted with normal.

^cDiabetic contrasted with normal.

^dTest of significance for relative risk equal to 1 (current dioxin and time categorized).

[†]Overall test of independence of current dioxin and 2-hour postprandial glucose within time stratum.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

M vs. L: Medium current dioxin category versus low current dioxin category.

H vs. L: High current dioxin category versus low current dioxin category.

TABLE 15-18. (Continued)
Analysis of 2-Hour Postprandial Glucose
(Discrete)

Ranch Hands - Current Dioxin (Categorized) and Time - Adjusted					
Assumption	Time (Yrs.)	Current Dioxin Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
g) Minimal (n=467)	≤18.6	C-by-T ^a		0.358	AGE (p=0.007) RACE (p=0.138) %BFAT (p<0.001)
		Overall [†]		0.177	
		M vs. L ^b	1.51 (0.60,3.82)	0.387 ^d	
		H vs. L ^b	1.22 (0.37,4.02)	0.748 ^d	
		M vs. L ^c	1.14 (0.16,7.88)	0.895 ^d	
		H vs. L ^c	5.20 (0.82,32.91)	0.080 ^d	
	>18.6	Overall [†]		0.140	
		M vs. L ^b	0.46 (0.21,0.97)	0.040 ^d	
		H vs. L ^b	0.53 (0.22,1.27)	0.154 ^d	
		M vs. L ^c	0.53 (0.08,3.71)	0.525 ^d	
h) Maximal (n=678)	≤18.6	C-by-T ^a		0.813	AGE (p<0.001) RACE (p=0.054) %BFAT (p<0.001)
		Overall [†]		0.102	
		M vs. L ^b	1.19 (0.61,2.34)	0.616 ^d	
		H vs. L ^b	0.99 (0.36,2.70)	0.988 ^d	
		M vs. L ^c	1.14 (0.23,5.62)	0.870 ^d	
		H vs. L ^c	5.33 (1.22,23.28)	0.026 ^d	
	>18.6	Overall [†]		0.518	
		M vs. L ^b	0.97 (0.52,1.83)	0.933 ^d	
		H vs. L ^b	1.17 (0.55,2.49)	0.686 ^d	
		M vs. L ^c	0.51 (0.11,2.29)	0.381 ^d	
		H vs. L ^c	1.93 (0.52,7.22)	0.329 ^d	

^aOverall test of significance of current dioxin-by-time interaction.

^bImpaired contrasted with normal.

^cDiabetic contrasted with normal.

^dTest of significance for relative risk equal to 1 (current dioxin and time categorized).

[†]Overall test of independence of current dioxin and 2-hour postprandial glucose within time stratum.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

M vs. L: Medium current dioxin category versus low current dioxin category.

H vs. L: High current dioxin category versus low current dioxin category.

TABLE 15-18. (Continued)
Analysis of 2-Hour Postprandial Glucose
(Discrete)

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

Current Dioxin Category	n	Percent			Contrast	Impaired versus Normal		Diabetic versus Normal	
		Normal	Impaired	Diabetic		Est. Relative Risk (95% C.I.)	p-Value	Est. Relative Risk (95% C.I.)	p-Value
Background	740	82.4	14.6	3.0					
Unknown	331	83.7	14.5	1.8	Unknown vs. Background	0.98 (0.68,1.41)	0.907	0.60 (0.24,1.50)	0.275
Low	179	83.2	15.6	1.1	Low vs. Background	1.06 (0.37,1.67)	0.795	0.37 (0.09,1.60)	0.185
High	166	78.3	15.7	6.0	High vs. Background	1.13 (0.71,1.80)	0.610	2.14 (0.99,4.62)	0.053
Total	1,416								

All categories: p=0.174

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

Current Dioxin Category	n	Contrast	Impaired versus Normal		Diabetic versus Normal		Covariate Remarks
			Adj. Relative Risk (95% C.I.)	p-Value	Adj. Relative Risk (95% C.I.)	p-Value	
Background	705						AGE (p<0.001) RACE (p=0.142) %BFAT (p<0.001) PERS (p=0.092)
Unknown	314	Unknown vs. Background	1.03 (0.71,1.51)	0.872	0.88 (0.37,2.06)	0.760	
Low	175	Low vs. Background	1.10 (0.70,1.73)	0.685	0.60 (0.19,1.89)	0.386	
High	160	High vs. Background	1.41 (0.87,2.27)	0.160	2.35 (1.06,5.19)	0.035	
Total	1,354						

All categories: p=0.267

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

to the low current dioxin category under the minimal assumption (Adj. RR=0.46, 95% C.I.: [0.21,0.97], p=0.040).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of categorized current dioxin was not significant for discretized 2-hour postprandial glucose (Table 15-18 [i]: p=0.174), although the high versus background contrast indicated a marginal risk of diabetic glucose levels (Est. RR=2.14, 95% C.I.: [0.99,4.62], p=0.053).

Adjusting for age, race, percent body fat, and personality type, the overall current dioxin effect remained nonsignificant (Table 15-18 [j]: p=0.267), and the risk of a diabetic glucose level became significant for the high versus background contrast (Adj. RR=2.35, 95% C.I.: [1.06,5.19], p=0.035). The overall current dioxin effect became marginally significant with percent body fat excluded from the model (Appendix Table N-2: p=0.092).

Composite Diabetes Indicator

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

Under both the minimal and maximal assumptions, the unadjusted analysis of the composite diabetes indicator revealed a significant positive association with initial dioxin (Table 15-19 [a] and [b]: p=0.023 and p<0.001, respectively). The estimated relative risk of diabetes for a twofold increase in initial dioxin was 1.27 for the minimal cohort and 1.33 for the maximal cohort. The percentage of Ranch Hands with a verified history of diabetes or a 2-hour postprandial glucose level above 200 mg/dl increased with initial dioxin under both assumptions (minimal: 10.1%, 12.5%, and 14.5% for the low, medium, and high initial dioxin categories; maximal: 5.4%, 10.6%, and 16.7% for the low, medium, and high initial dioxin categories).

Under both assumptions, the association became stronger after covariate adjustment. The relative risk was 1.46 (p=0.001) for the minimal analysis, adjusting for age and percent body fat. For the maximal analysis, the relative risk was 1.48 (p<0.001) after adjusting for age, race, and percent body fat.

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

The current dioxin and time since tour analyses of the composite diabetes indicator failed to detect a significant current dioxin-by-time interaction for both the minimal and maximal assumptions (Table 15-19 [e-h]: p>0.50 for all analyses). However, in most time strata, current dioxin was significantly associated with an increased risk of diabetes. This finding is consistent with the results for model 1, which found a significant association between initial dioxin and the composite diabetes indicator, because initial dioxin and current dioxin are highly correlated.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of categorized current dioxin was highly significant for the composite diabetes indicator (Table 15-19 [i]: p<0.001). The high current dioxin category had more than twice as many diabetics as the background category (16.6% versus 8.2%,

TABLE 15-19.

Analysis of Composite Diabetes Indicator

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Diabetic	Est. Relative Risk (95% C.I.)^a	p-Value
a) Minimal (n=517)	Low	129	10.1	1.27 (1.04,1.56)	0.023
	Medium	257	12.5		
	High	131	14.5		
b) Maximal (n=738)	Low	185	5.4	1.33 (1.13,1.55)	<0.001
	Medium	367	10.6		
	High	186	16.7		
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.)^a		p-Value	Covariate Remarks	
c) Minimal (n=517)	1.46 (1.17,1.82)		0.001	AGE (p<0.001) %BFAT (p=0.003)	
d) Maximal (n=738)	1.48 (1.23,1.77)		<0.001	AGE (p<0.001) RACE (p=0.099) %BFAT (p<0.001)	

^aRelative 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 15-19. (Continued)

Analysis of Composite Diabetes Indicator

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Diabetic/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=517)	≤18.6	13.9 (72)	9.4 (127)	13.0 (54)	1.13 (0.80,1.61)	0.527 ^b 0.488 ^c
	>18.6	10.5 (57)	12.3 (130)	16.9 (77)	1.30 (1.00,1.69)	0.047 ^c
f) Maximal (n=738)	≤18.6	2.8 (106)	9.5 (190)	16.9 (83)	1.34 (1.03,1.74)	0.638 ^b 0.027 ^c
	>18.6	8.9 (79)	11.9 (176)	16.3 (104)	1.24 (1.01,1.52)	0.040 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
g) Minimal (n=517)	≤18.6	1.46 (0.99,2.13)	0.723 ^b 0.054 ^c	AGE (p<0.001) %BFAT (p=0.003)
	>18.6	1.58 (1.18,2.11)	0.002 ^c	
h) Maximal (n=738)	≤18.6	1.62 (1.20,2.19)	0.512 ^b 0.002 ^c	AGE (p<0.001) RACE (p=0.089) %BFAT (p<0.001)
	>18.6	1.43 (1.14,1.81)	0.002 ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest 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 15-19. (Continued)
Analysis of Composite Diabetes Indicator

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

Current Dioxin Category	n	Percent Diabetic	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	782	8.2	All Categories		<0.001
Unknown	344	5.5	Unknown vs. Background	0.66 (0.39,1.11)	0.118
Low	193	8.3	Low vs. Background	1.01 (0.57,1.80)	0.962
High	187	16.6	High vs. Background	2.23 (1.40,3.54)	0.001
Total	1,506				

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		0.003**	DXCAT*AGE (p=0.012) %BFAT (p<0.001)
Unknown	344	Unknown vs. Background	0.82 (0.48,1.43)**	0.491**	
Low	193	Low vs. Background	1.01 (0.56,1.82)**	0.986**	
High	187	High vs. Background	2.51 (1.51,4.16)**	<0.001**	
Total	1,506				

**Categorized current dioxin-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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=0.001). The incidence of diabetes in both the unknown (5.5%) and low (8.3%) categories was not significantly different from the background incidence.

The adjusted analysis detected a significant categorized current dioxin-by-age interaction (Table 15-19 [j]: p=0.012) for the composite diabetes indicator. Stratified analyses were done to explore the interaction. They showed that the incidence of diabetes differed significantly among the four current dioxin categories for older participants (Appendix Table N-1: born before 1942: p=0.002), but the overall current dioxin effect was not significant for younger participants (born in or after 1942: p=0.595). For older participants, the percentages of diabetics were 10.2, 6.6, 12.4, and 28.6 percent for the background, unknown, low, and high current dioxin categories. Adjusting for percent body fat, older Ranch Hands in the high current dioxin category were more than three times as likely to be positive for diabetes than similar-aged Comparisons in the background category (Adj. RR=3.09, 95% C.I.: [1.64,5.82], p<0.001). The high versus background relative risk was greater than 1, but not significant, for younger individuals (Adj. RR=1.49, 95% C.I.: [0.65,3.41], p=0.341). The percentages of younger participants with diabetes were 5.3, 3.4, 2.5, and 9.4 percent for the background, unknown, low, and high current dioxin categories.

Excluding percent body fat from the model, the high versus background relative risk of diabetes increased to 3.52 for the older age stratum (Appendix Table N-3: 95% C.I.: [1.93,6.42], p<0.001) and became 1.86 for the younger age stratum (95% C.I.: [0.84,4.09], p=0.125). The incidences of diabetes in the unknown and low categories were not significantly different from the background incidence in either age stratum.

The adjusted results were comparable to the unadjusted findings after excluding the interaction. Adjusting for age and percent body fat, the overall current dioxin effect was significant (Table 15-19 [j]: p=0.003) and the high versus background contrast was highly significant (Adj. RR=2.51, 95% C.I.: [1.51,4.16], p<0.001). The association became even stronger when percent body fat was dropped from the model. For this analysis, the overall current dioxin effect was highly significant (Appendix Table N-2: p<0.001), the unknown versus background contrast became marginally less than 1 (Adj. RR=0.63, 95% C.I.: [0.37,1.08], p=0.095), and the adjusted relative risk for the high versus background contrast was 2.95 (95% C.I.: [1.82,4.79], p<0.001).

Longitudinal Analysis

Laboratory Examination Variables

Longitudinal analyses were conducted to evaluate the association between various measures of dioxin (initial dioxin, current dioxin and time since tour, and categorized current dioxin) and the change between the 1982 Baseline examination and the 1987 examination in T₃ % uptake, TSH, and testosterone. T₃ % uptake and testosterone were treated as continuous variables. TSH was analyzed in its discrete form because laboratory techniques to measure TSH differed between examinations.

For a specific longitudinal analysis of T₃ % uptake or testosterone (e.g., minimal assumption, initial dioxin analysis), the left side of each subpanel of a table provides the means and sample sizes at each examination for participants who were compliant at both the 1982 and 1987 examinations. Based on the difference between 1987 and 1982 laboratory

values, the right side of each subpanel presents slopes, standard errors, and associated p-values (for models using initial dioxin or models using current dioxin and time), or differences of examination mean changes, 95 percent confidence intervals, and associated p-values (for models using categorized current dioxin).

For a specific longitudinal analysis of TSH, the upper part of each subpanel of a table provides the percents of participants with abnormally high levels of TSH at each examination. The lower part of each subpanel presents sample sizes, percents, relative risks, and associated 95 percent confidence intervals for all participants who had normal TSH levels at the 1982 examination and who were compliant at the 1987 examination.

T₃ % Uptake (Continuous)

Table 15-20 presents the results of the longitudinal analyses for T₃ % uptake (unadjusted for covariate information).

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

Under both the minimal and the maximal assumptions, the longitudinal analysis displayed a nonsignificant negative association between initial dioxin and the change (as measured by the difference from the 1987 examination value relative to the 1982 examination value) in T₃ % uptake (Table 15-20 [a] and [b]: p=0.113 and p=0.699, respectively).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

For the longitudinal analysis of the change in T₃ % uptake between 1982 and 1987, the interaction between current dioxin and time since tour was not significant under both the minimal and the maximal assumptions (Table 15-20 [c] and [d]: p=0.300 and p=0.167). For the minimal cohort, there was a marginally significant decreasing association between current dioxin and the change in T₃ % uptake for Ranch Hands with more than 18.6 years since the end of their tour (Table 15-20 [d]: p=0.073).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The analysis of categorized current dioxin found a significant overall difference in the mean change in T₃ % uptake (between 1982 and 1987) among the four current dioxin categories (Table 15-20 [e]: p=0.018). The differences between the mean change in T₃ % uptake of the unknown, low, and high categories versus the mean change for those in the background category were -0.3, 0.2, and -0.4 percent, respectively. The mean change in T₃ % uptake for the Comparisons in the background group was significantly greater than the mean change for the Ranch Hands in the low current dioxin category (p=0.036). Also, the difference in the mean change in T₃ % uptake for the background and high current dioxin categories was marginally significant (p=0.055).

TSH (Discrete)

The longitudinal analyses of TSH were based on participants who had a normal level of TSH in 1982 (see Chapter 4). Table 15-21 presents the results of the longitudinal analyses for TSH (unadjusted for covariate information). Due to an inconsistency in the laboratory technique, the normal/abnormal cutpoint for TSH differed at each examination. The cutpoints

TABLE 15-20.
Longitudinal Analysis of T₃ % Uptake
(Continuous)

Ranch Hands - Log₂ (Initial Dioxin)						
Assumption	Initial Dioxin	<u>Mean^a/(n) Examination</u>			Slope (Std. Error)^b	p-Value
		1982	1985	1987		
a) Minimal (R ² =0.005)	Low	30.1 (122)	27.8 (120)	30.5 (122)	-0.0044 (0.0028)	0.113
	Medium	29.9 (251)	27.6 (246)	30.3 (251)		
	High	29.9 (121)	27.5 (120)	30.1 (121)		
b) Maximal (R ² <0.001)	Low	30.5 (169)	27.8 (166)	30.6 (169)	-0.0008 (0.0021)	0.699
	Medium	30.0 (352)	27.8 (345)	30.5 (352)		
	High	29.9 (173)	27.5 (171)	30.0 (173)		

^aTransformed from natural logarithm scale.

^bSlope and standard error based on difference between natural logarithm of 1987 T₃ % uptake and natural logarithm of 1982 T₃ % uptake versus log₂ 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.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 15-20. (Continued)
Longitudinal Analysis of T₃ % Uptake
(Continuous)

Ranch Hands - Log ₂ (Current Dioxin) and Time								
Assumption	Time (Yrs.)	Examination	Mean ^a /(n) Current Dioxin			Slope (Std. Error) ^b	p-Value	
			Low	Medium	High			
c) Minimal (R ² =0.010)	≤18.6	1982	29.9 (67)	29.9 (123)	30.1 (51)	-0.0006 (0.0045)	0.300 ^c 0.896 ^d	
		1985	27.5 (66)	27.8 (120)	27.8 (50)			
		1987	30.2 (67)	30.6 (123)	30.5 (51)			
	>18.6	1982	30.1 (55)	29.9 (128)	29.8 (70)		-0.0067 (0.0037)	0.073 ^d
		1985	28.2 (54)	27.4 (126)	27.3 (70)			
		1987	31.0 (55)	30.0 (128)	29.9 (70)			
d) Maximal (R ² =0.004)	≤18.6	1982	30.6 (95)	29.9 (182)	30.1 (78)	0.0029 (0.0032)	0.167 ^c 0.372 ^d	
		1985	27.8 (92)	27.8 (178)	27.7 (77)			
		1987	30.7 (95)	30.5 (182)	30.5 (78)			
	>18.6	1982	30.4 (74)	30.0 (169)	30.0 (96)		-0.0031 (0.0029)	0.280 ^d
		1985	27.8 (73)	27.8 (167)	27.3 (95)			
		1987	30.6 (74)	30.5 (169)	29.7 (96)			

^aTransformed from natural logarithm scale.

^bSlope and standard error based on difference between natural logarithm of 1987 T₃ % uptake and natural logarithm of 1982 T₃ % uptake versus log₂ dioxin.

^cTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^dTest of significance for slope equal to 0 (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.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 15-20. (Continued)
Longitudinal Analysis of T₃ % Uptake
(Continuous)

e) Ranch Hands and Comparisons by Current Dioxin Category							
Current Dioxin Category	<u>Mean^a/(n) Examination</u>			Contrast	Difference of Examination Mean Change (95% C.I.) ^e		p-Value ^f
	1982	1985	1987		--	--	
Background	30.2 (674)	27.7 (670)	30.6 (674)	All Categories			0.018
Unknown	30.6 (310)	27.9 (304)	30.6 (310)	Unknown vs. Background	-0.3	--	0.036
Low	29.8 (190)	27.6 (187)	30.4 (190)	Low vs. Background	0.2	--	0.291
High	30.0 (174)	27.5 (172)	30.1 (174)	High vs. Background	-0.4	--	0.055
(R ² =0.007)							

^aTransformed from natural logarithm scale.

^eDifference of 1987 and 1982 examination mean changes after transformation to original scale; confidence interval on difference of 1987 and 1982 examination mean changes not given because analysis was performed on natural logarithm scale.

^fP-value is based on difference of 1987 and 1982 examination mean changes 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.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 15-21.
Longitudinal Analysis of TSH
(Discrete)

Ranch Hands - Log₂ (Initial Dioxin)				
Assumption	Initial Dioxin	Percent Abnormal/(n) Examination		
		1982	1985	1987
a) Minimal	Low	0.0 (122)	0.0 (120)	0.0 (122)
	Medium	1.2 (251)	1.2 (246)	2.4 (251)
	High	0.8 (121)	0.8 (120)	3.3 (121)
<u>Normal in 1982</u>				
Initial Dioxin	n in 1987	Percent Abnormal in 1987	Est. Relative Risk (95% C.I.) ^a	p-Value
Low	122	0.0	1.18 (0.63,2.20)	0.613
Medium	248	1.2		
High	120	2.5		

^aRelative 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.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 15-21. (Continued)
Longitudinal Analysis of TSH
(Discrete)

Ranch Hands - Log₂ (Initial Dioxin)				
Assumption	Initial Dioxin	Percent Abnormal/(n) Examination		
		1982	1985	1987
b) Maximal	Low	0.6 (169)	0.0 (166)	3.6 (169)
	Medium	0.9 (352)	0.6 (345)	1.4 (352)
	High	1.2 (173)	1.2 (171)	2.9 (173)
<hr/> Normal in 1982 <hr/>				
Initial Dioxin	n in 1987	Percent Abnormal in 1987	Est. Relative Risk (95% C.I.)^a	p-Value
Low	168	3.0	0.87 (0.55,1.40)	0.567
Medium	349	0.9		
High	171	1.8		

^aRelative 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.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 15-21. (Continued)
Longitudinal Analysis of TSH
(Discrete)

Ranch Hands - Log₂ (Current Dioxin) and Time					
Assumption	Time (Yrs.)	Examination	Percent Abnormal/(n) Current Dioxin		
			Low	Medium	High
c) Minimal	≤18.6	1982	0.0 (68)	1.6 (123)	0.0 (51)
		1985	0.0 (67)	1.7 (120)	0.0 (50)
		1987	0.0 (68)	2.4 (123)	2.0 (51)
	>18.6	1982	0.0 (54)	0.8 (128)	1.4 (70)
		1985	0.0 (53)	0.8 (126)	1.4 (70)
		1987	1.9 (54)	1.6 (128)	4.3 (70)

Time (Yrs.)	Normal in 1982: Percent Abnormal/(n) in 1987 Current Dioxin			Est. Relative Risk (95% C.I.)^a	p-Value
	Low	Medium	High		
≤18.6	0.0 (68)	0.8 (121)	2.0 (51)	1.31 (0.40,4.30)	0.691 ^b 0.652 ^c
>18.6	1.9 (54)	0.8 (127)	2.9 (69)	0.98 (0.44,2.18)	0.961 ^c

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 15-21. (Continued)
Longitudinal Analysis of TSH
(Discrete)

Ranch Hands - Log₂ (Current Dioxin) and Time					
Assumption	Time (Yrs.)	Examination	Percent Abnormal/(n) Current Dioxin		
			Low	Medium	High
d) Maximal	≤18.6	1982	0.0 (95)	0.0 (183)	2.6 (78)
		1985	0.0 (92)	0.0 (179)	2.6 (77)
		1987	2.1 (95)	0.6 (183)	3.9 (78)
	>18.6	1982	2.7 (74)	0.6 (168)	1.0 (96)
		1985	0.0 (73)	0.6 (166)	1.1 (95)
		1987	5.4 (74)	1.8 (168)	3.1 (96)

Time (Yrs.)	Normal in 1982: Percent Abnormal/(n) in 1987 Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
	Low	Medium	High		
≤18.6	2.1 (95)	0.6 (183)	1.3 (76)	0.89 (0.38,2.09)	0.769 ^b 0.792 ^c
>18.6	4.2 (72)	1.2 (167)	2.1 (95)	0.76 (0.41,1.42)	0.387 ^c

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

Statistical analyses are based only on participants who changed status between 1982 and 1987 (see Chapter 4, Statistical Methods).

TABLE 15-21. (Continued)
Longitudinal Analysis of TSH
(Discrete)

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	Percent Abnormal/(n) Examination		
	1982	1985	1987
Background	1.0 (674)	0.6 (670)	2.1 (674)
Unknown	1.0 (310)	0.3 (304)	2.9 (310)
Low	0.5 (190)	0.5 (187)	1.6 (190)
High	1.7 (174)	1.7 (172)	3.5 (174)

Normal in 1982

Current Dioxin Category	n in 1987	Percent Abnormal in 1987	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	667	1.2	All Categories		0.598
Unknown	307	2.3	Unknown vs. Background	1.92 (0.69,5.35)	0.211
Low	189	1.1	Low vs. Background	0.88 (0.19,4.18)	0.873
High	171	1.8	High vs. Background	1.47 (0.39,5.60)	0.572

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.
 Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

were 10.0 μ IU/ml at the 1982 Baseline examination, 7.5 μ IU/ml for the 1985 examination, and 3.0 μ IU/ml for the 1987 examination.

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

Under the minimal and the maximal assumptions, the longitudinal analysis exhibited a nonsignificant association between initial dioxin and the percentage of Ranch Hands with abnormal TSH levels at the 1987 examination (Table 15-21 [a] and [b]: $p=0.613$ and $p=0.567$, respectively).

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

The longitudinal analysis of current dioxin and time since tour and the proportion of Ranch Hands with abnormal TSH levels at the 1987 examination found no significant current dioxin-by-time interaction under either the minimal or the maximal assumption (Table 15-21 [c] and [d]: $p=0.691$ and $p=0.769$).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The percentages of participants with abnormal TSH levels at the 1987 followup examination did not differ significantly among the four current dioxin categories (Table 15-21 [e]: $p=0.598$).

Testosterone (Continuous)

Table 15-22 presents the results of the longitudinal analyses of testosterone (unadjusted for covariate information).

Model 1: Ranch Hands – Log₂ (Initial Dioxin)

The analysis of the change in the testosterone levels of Ranch Hands between the 1982 and 1987 examinations displayed a marginally significant positive association with initial dioxin under both the minimal and the maximal assumptions (Table 15-22 [a] and [b]: $p=0.076$ and $p=0.072$, respectively). Thus, the difference in the 1987 examination testosterone level of Ranch Hands relative to the 1982 examination level increased for increasing levels of initial dioxin.

Model 2: Ranch Hands – Log₂ (Current Dioxin) and Time

Based on the minimal assumption, the longitudinal analysis of the change in testosterone did not find a significant interaction between current dioxin and time since tour (Table 15-22 [c]: $p=0.899$). However, for Ranch Hands with more than 18.6 years since the end of their tour, there was a significant positive association between their current dioxin levels and the change in their testosterone levels between the 1982 and 1987 examinations ($p=0.048$).

For the maximal cohort, the interaction between current dioxin and time since tour was not significant (Table 15-22 [d]: $p=0.851$). The positive association between the change in testosterone levels and current dioxin exposure was marginally significant for Ranch Hands in both time strata (≤ 18.6 years: $p=0.079$; >18.6 years: $p=0.084$).

TABLE 15-22.
Longitudinal Analysis of Testosterone (ng/dl)
(Continuous)

Ranch Hands - Log₂ (Initial Dioxin)						
Assumption	Initial Dioxin	Mean ^a /(n) Examination			Slope (Std. Error) ^b	p-Value
		1982	1985	1987		
a) Minimal (R ² =0.006)	Low	645.3 (122)	570.1 (119)	514.3 (122)	0.2211 (0.1241)	0.076
	Medium	624.5 (252)	565.9 (247)	522.5 (252)		
	High	603.6 (125)	598.5 (124)	508.8 (125)		
b) Maximal (R ² =0.005)	Low	647.1 (170)	619.1 (167)	531.9 (170)	0.1618 (0.0898)	0.072
	Medium	631.8 (354)	573.3 (345)	519.1 (354)		
	High	613.2 (179)	585.2 (177)	511.5 (179)		

^aTransformed from square root scale.

^bSlope and standard error based on difference between square root of 1987 testosterone and square root of 1982 testosterone versus log₂ 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.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 15-22. (Continued)
Longitudinal Analysis of Testosterone (ng/dl)
(Continuous)

Ranch Hands - Log₂ (Current Dioxin) and Time							
Assumption	Time (Yrs.)	Examination	Mean^a/(n) Current Dioxin			Slope (Std. Error)^b	p-Value
			Low	Medium	High		
c) Minimal							
(R ² =0.017)	≤18.6	1982	657.7 (68)	616.8 (124)	616.4 (52)	0.2947 (0.2007)	0.899 ^c 0.143 ^d
		1985	559.9 (67)	570.5 (121)	624.9 (51)		
		1987	521.8 (68)	542.1 (124)	516.2 (52)		
	>18.6	1982	620.8 (54)	638.9 (128)	589.4 (73)	0.3277 (0.1650)	0.048 ^d
		1985	551.1 (52)	573.5 (126)	582.5 (73)		
		1987	497.0 (54)	505.3 (128)	506.9 (73)		
d) Maximal							
(R ² =0.012)	≤18.6	1982	662.7 (94)	635.1 (183)	608.4 (80)	0.2460 (0.1400)	0.851 ^c 0.079 ^d
		1985	635.2 (91)	576.1 (179)	592.1 (79)		
		1987	544.4 (94)	531.2 (183)	525.0 (80)		
	>18.6	1982	627.0 (76)	636.7 (170)	603.7 (100)	0.2111 (0.1220)	0.084 ^d
		1985	593.5 (74)	576.1 (167)	575.1 (99)		
		1987	506.9 (76)	507.1 (170)	506.7 (100)		

^aTransformed from square root scale.

^bSlope and standard error based on difference between square root of 1987 testosterone and square root of 1982 testosterone versus log₂ dioxin.

^cTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^dTest of significance for slope equal to 0 (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.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 15-22. (Continued)

**Longitudinal Analysis of Testosterone (ng/dl)
(Continuous)**

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	Mean ^a /(n) Examination			Contrast	Difference of Examination Mean Change (95% C.I.) ^e		p-Value ^f
	1982	1985	1987				
Background	619.0 (685)	574.0 (679)	520.2 (685)	All Categories			0.641
Unknown	663.3 (315)	632.6 (308)	551.5 (315)	Unknown vs. Background	-13.0	--	0.335
Low	628.1 (189)	582.9 (186)	525.8 (189)	Low vs. Background	-3.5	--	0.811
High	605.8 (180)	582.6 (178)	514.8 (180)	High vs. Background	7.8	--	0.560

(R²=0.001)

^aTransformed from square root scale.

^eDifference of 1987 and 1982 examination mean changes after transformation to original scale; confidence interval on difference of 1987 and 1982 examination mean changes not given because analysis was performed on square root scale.

^fP-value is based on difference of 1987 and 1982 examination mean changes on square root 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.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The change in testosterone levels between the 1982 and 1987 examinations did not differ significantly among participants in the four current dioxin categories (Table 15-22 [e]: $p=0.641$).

DISCUSSION

The historical, physical examination, and laboratory data analyzed in the current assessment provide a valid reflection of thyroid, gonadal, and glucoregulatory pancreatic functions by simple indices that are well established in clinical practice. Additional physical findings—percent body fat, ocular/funduscopy, integumentary, and deep tendon reflexes—were relevant to the clinical evaluation of endocrine function (4). These variables are discussed in other chapters of the current report.

Of the two thyroid laboratory variables examined, the T_3 % uptake, though less sensitive than the serum TSH, assumes importance as the only index common to all three physical examination cycles of the Air Force Health Study. In lacking a lower limit of normal, the radioimmunoassay technique of serum TSH determination employed in the current study may not be sensitive to hyperthyroid states. As a test used in the last two examination cycles, however, it serves as a valid index for contrasting the Ranch Hand and Comparison cohorts over time.

Several of the variables analyzed revealed statistically significant effects related to the body burden of dioxin, though in most instances the clinical significance is limited or uncertain. Dimensional criteria are available to assess testicular size, but rarely are used in practice. At the 1987 physical examination, the determination of testicular abnormality involved subjective judgement on the part of each examiner in distinguishing between normal/small and abnormal/atrophic; there was no attempt to account for prior testicular trauma or infection (e.g., mumps). Analyses were done that showed no statistical difference among examiners in their testicular evaluations (the percentages of abnormalities indicated by the five examiners were 1.8 percent [7/395], 3.9 percent [17/439], 2.9 percent [12/412], 0 percent [0/3], and 3.6 percent [15/421]). On the physical examination, unilateral atrophy of a testicle was noted as a relatively common finding. There were 9 assayed participants with a bilateral testicular abnormality, 16 with a left testicular abnormality, and 26 with a right testicular abnormality.

Because of the wide variation in testicular size in the normal population, the determination of serum testosterone must be considered a more reliable index than palpation of the testes. Although the prevalence of testes abnormalities was associated significantly with both initial and current dioxin, the discrete analyses of testosterone did not find a significant association between dioxin and abnormally low levels of serum testosterone. However, for the continuous analyses of testosterone, a significant decrease was noted in association with increasing initial serum dioxin levels when percent body fat was excluded from the model. Categorizing initial dioxin, the differences between the mean serum testosterone for the low, medium, and high categories (559.9, 544.3, and 508.5 ng/dl) are not considered clinically relevant.

In the analysis of thyroid function, slight differences were found in the serum TSH and T_3 % uptake indices consistent with a dose response effect for initial or categorized current

dioxin. A slightly higher mean serum TSH was noted in the high versus background current dioxin categories (1.026 μ IU/ml versus 0.920 μ IU/ml) and a slightly lower mean T₃ % uptake in the high versus background groups (29.99 percent versus 30.65 percent). Though these results are internally consistent with subtle decreases in thyroid function related to dioxin exposure, they cannot be considered physiologically significant. Further, by discrete analysis of the thyroid indices, there were no detectable differences in thyroid function related to dioxin.

Analysis of the indices of glucose metabolism revealed a statistically significant association between 2-hour postprandial glucose and initial dioxin. The mean levels for the low, medium, and high initial dioxin categories (108.0, 111.6, and 115.8 mg/dl) were well within normal limits. Though a difference of 7.8 mg/dl between the high and low categories is not considered clinically significant, the data are consistent with a dose-response effect. Further, because the differences were more pronounced in those participants further removed from service in Southeast Asia (>18.6 years), the possibility of a temporal effect is raised. The analyses of fasting glucose were also significant. Ranch Hand participants with the highest levels of serum dioxin were nearly three times as likely to have elevated fasting blood sugars as Comparisons. More important, perhaps, is the significant association between dioxin and the incidence of overt diabetes by verified history or by a 2-hour postprandial blood sugar of more than 200 mg/dl. The apparent association of glucose intolerance with the body burden of dioxin has been noted in a previous study, although the mechanism has not been defined (21). Under the maximal assumption, more than a threefold increase in the incidence of diabetes was found in the high versus the low initial dioxin categories (16.7% versus 5.4%).

SUMMARY

Table 15-23 summarizes the results of the initial dioxin analyses for the 10 variables examined in 1987 to assess the endocrine system. Table 15-24 presents the results for the current dioxin and time since tour analyses, and Table 15-25 displays the results of the categorized current dioxin analyses.

Questionnaire Variables

Two variables were constructed from the review of systems and the health interval questionnaire to determine the status of each participant's thyroid. For all three sets of analyses, there was no evidence of a dioxin association with either the response to current thyroid function or with the verified response to a history of thyroid disease.

Physical Examination Variables

The thyroid gland and the testes were evaluated at the physical examination. None of the results for the thyroid gland analyses was significant. Several of the testes analyses displayed significant associations between dioxin and unilateral atrophy of a testicle, although the number of study participants with bilateral atrophy or absence was equivalent between the total Ranch Hand and Comparison groups (nine in each group).

The adjusted initial dioxin analyses found a significant increased risk of testes abnormalities under both the minimal and maximal assumptions. The association between current dioxin and abnormal testes did not significantly differ between time since tour strata, but the adjusted relative risk was significant for Ranch Hands with a later tour under both

TABLE 15-23.
Summary of Initial Dioxin Analyses for Endocrine Variables
Based on Minimal and Maximal Assumptions
(Ranch Hands Only)

Variable	Unadjusted		Adjusted	
	Minimal	Maximal	Minimal	Maximal
Questionnaire				
Current Thyroid Function (Self-Administered) (D)	ns	ns	ns	ns
History of Thyroid Disease (Interviewer-Administered) (D)	NS	NS	NS	NS
Physical Examination				
Thyroid Gland (D)	ns	NS	ns	NS
Testes (D)	NS	NS*	+0.017	+0.003
Laboratory				
T ₃ % Uptake (C)	-0.042	-0.002	-0.034	-0.003
T ₃ % Uptake (D)	ns	ns	ns	ns
TSH (C)	ns	ns	ns	NS
TSH (D)	NS	NS	NS	NS
FSH (C)	ns	ns	NS	NS
FSH (D)	NS	NS	NS	NS
Testosterone ^a (C)	ns	ns	** (ns)	** (ns)
Testosterone ^{a,b} (C)	--	--	** (-0.023)	** (<0.001)
Testosterone (D)	ns	NS	ns	NS
Fasting Glucose (C)	+0.027	+<0.001	+<0.001	+<0.001
Fasting Glucose (D)	+0.022	+<0.001	+<0.001	+<0.001
2-Hour Postprandial Glucose (C)	NS	+0.021	** (NS)	NS
2-Hour Postprandial Glucose ^b (C)	--	--	+0.020	+0.003
2-Hour Postprandial Glucose (D)	NS	NS	NS	NS
Composite Diabetes Indicator (C)	+0.023	+<0.001	+0.001	+<0.001

^aNegative slope considered adverse for this variable.

^bAdjusted results from models without percent body fat presented for this variable; see Appendix Table N-2 for a detailed description of these analyses.

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.

-: Slope negative.

--: Not applicable.

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

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

** (NS)/**(ns): Log₂ (initial dioxin)-by-covariate interaction ($p \leq 0.05$); not significant when interaction is deleted; refer to Appendix Table N-1 for a detailed description of this interaction.

** (...): Log₂ (initial dioxin)-by-covariate interaction ($p \leq 0.05$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table N-1 for a detailed description of this interaction.

Note: P-value given if $p \leq 0.05$.

Table N-2 contains detailed analyses for models without percent body fat.

A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis; a capital "NS" for FSH and 2-hour postprandial glucose does not imply directionality due to log-linear analysis.

TABLE 15-24.

**Summary of Current Dioxin and Time Analyses for Endocrine Variables
Based on Minimal and Maximal Assumptions
(Ranch Hands Only)**

Variable	C*T	Unadjusted		C*T	Unadjusted	
		Minimal	Maximal		Minimal	Maximal
		≤18.6	>18.6		≤18.6	>18.6
Questionnaire						
Current Thyroid Function (Self-Administered) (D)	NS	ns	NS	ns	ns	ns
History of Thyroid Disease (Interviewer-Administered) (D)	NS	ns	NS	ns	ns	ns
Physical Examination						
Thyroid Gland (D)	NS	ns	ns	NS	NS	NS
Testes (D)	ns	NS	NS	ns	NS	NS
Laboratory						
T ₃ % Uptake (C)	ns*	NS	-0.016	ns	ns	-0.003
T ₃ % Uptake (D)	ns	ns	ns	ns	ns	ns
TSH (C)	ns	NS	ns	ns	ns	ns
TSH (D)	ns	NS	NS	ns	NS	ns
FSH (C)	NS*	-0.014	ns	+0.014	-0.007	NS
FSH (D)	NS	NS	NS	NS*	NS	NS
Testosterone ^a (C)	NS	ns	NS	NS	ns	NS
Testosterone (D)	ns	ns	ns	ns	NS	ns
Fasting Glucose (C)	NS*	ns	+0.009	NS	NS	+0.002
Fasting Glucose (D)	NS	NS	+0.023	NS	NS	+0.006
2-Hour Postprandial Glucose (C)	ns	NS	NS	NS	NS	NS*
2-Hour Postprandial Glucose (D)	NS	NS	NS	NS	NS	NS
Composite Diabetes Indicator (D)	NS	NS	+0.047	ns	+0.027	+0.040

^aNegative slope considered adverse for this variable.

C: Continuous analysis.

D: Discrete analysis.

+: C*T: Relative risk/slope for ≤18.6 category less than relative risk/slope for >18.6 category.

≤18.6 and >18.6: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.

-: ≤18.6 and >18.6: Slope negative.

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

NS*/ns*: Marginally significant ($0.05 < p \leq 0.10$).

Note: P-value given if $p \leq 0.05$.

C*T: Log₂ (current dioxin)-by-time interaction hypothesis test.

≤18.6: Log₂ (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.

>18.6: Log₂ (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.

A capital "NS" denotes relative risk/slope for ≤18.6 category less than relative risk/slope for >18.6 category, relative risk 1.00 or greater for discrete analysis, or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk/slope for ≤18.6 category greater than relative risk/slope for >18.6 category, relative risk less than 1.00 for discrete analysis, or slope negative for continuous analysis; a capital "NS" for FSH and 2-hour postprandial glucose does not imply directionality due to log-linear analysis.

TABLE 15-24. (Continued)

**Summary of Current Dioxin and Time Analyses for Endocrine Variables
Based on Minimal and Maximal Assumptions
(Ranch Hands Only)**

Variable	C*T	Minimal		Adjusted		
		≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Current Thyroid Function (Self-Administered) (D)	NS	ns	NS	ns	ns	ns
History of Thyroid Disease (Interviewer-Administered) (D)	NS	ns	NS	ns	ns	ns
Physical Examination						
Thyroid Gland (D)	NS	ns	ns	NS	NS	NS
Testes (D)	ns	+0.006	NS	ns	+0.007	NS*
Laboratory						
T ₃ % Uptake (C)	-0.015	NS	-0.004	ns*	ns	-0.002
T ₃ % Uptake (D)	ns	ns	ns	ns	ns	ns
TSH (C)	ns	NS	ns	ns	NS	ns
TSH (D)	ns	NS	NS	** (ns)	** (NS)	** (ns)
FSH (C)	NS*	ns	NS	+0.011	ns	+0.015
FSH (D)	NS	NS	NS	0.047	NS	NS
Testosterone ^a (C)	NS	ns	ns	NS	ns	ns
Testosterone ^{a,b} (C)	NS	ns*	ns	NS	-0.012	ns*
Testosterone (D)	NS	ns	ns	ns	NS	ns
Fasting Glucose (C)	NS*	NS	+<0.001	** (NS)	** (+0.024)	** (+<0.001)
Fasting Glucose (D)	NS	NS	+<0.001	** (NS)	** (+0.007)	** (+<0.001)
2-Hour Postprandial Glucose (C)	** (ns)	** (NS)	** (NS)	NS	NS	NS*
2-Hour Postprandial Glucose ^b (C)	** (ns)	** (NS*)	** (NS)	NS	NS	+0.009
2-Hour Postprandial Glucose (D)	NS	NS	NS	NS	NS	NS
Composite Diabetes Indicator (D)	NS	NS*	+0.002	ns	+0.002	+0.002

^aNegative slope considered adverse for this variable.

^bAdjusted results from models without percent body fat presented for this variable; see Appendix Table N-2 for a detailed description of these analyses.

C: Continuous analysis.

D: Discrete analysis.

+: C*T: Slope for ≤18.6 category less than slope for >18.6 category.

≤18.6 and >18.6: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.

-: C*T: Slope for ≤18.6 category greater than slope for >18.6 category.

≤18.6 and >18.6: Relative risk less than 1.00 for discrete analysis; slope negative for continuous analysis.

NS/ns: Not significant (p>0.10).

NS*/ns*: Marginally significant (0.05<p≤0.10).

** (NS)/** (ns): Log₂ (current dioxin)-by-time-by-covariate interaction (p≤0.05); not significant when interaction is deleted; refer to Appendix Table N-1 for a detailed description of this interaction.

** (NS*): Log₂ (current dioxin)-by-time-by-covariate interaction (p≤0.05); marginally significant when interaction is deleted; refer to Appendix Table N-1 for a detailed description of this interaction.

** (...): Log₂ (current dioxin)-by-time-by-covariate interaction (0.05<p≤0.10); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table N-1 for a detailed description of this interaction.

TABLE 15-24. (Continued)

**Summary of Current Dioxin and Time Analyses for Endocrine Variables
Based on Minimal and Maximal Assumptions
(Ranch Hands Only)**

Note: P-value given if $p \leq 0.05$.

Appendix Table N-2 contains detailed analyses for models without percent body fat.

C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.

≤ 18.6 : Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.

> 18.6 : Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.

A capital "NS" denotes relative risk/slope for ≤ 18.6 category less than relative risk/slope for > 18.6 category, relative risk 1.00 or greater for discrete analysis, or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk/slope for ≤ 18.6 category greater than relative risk/slope for > 18.6 category, relative risk less than 1.00 for discrete analysis, or slope negative for continuous analysis; a capital "NS" for FSH and 2-hour postprandial glucose does not imply directionality due to log-linear analysis.

TABLE 15-25.

**Summary of Categorized Current Dioxin Analyses for
Endocrine Variables
(Ranch Hands and Comparisons)**

Variable	All	Unadjusted		
		Unknown versus Background	Low versus Background	High versus Background
Questionnaire				
Current Thyroid Function (Self-Administered) (D)	NS	NS	ns	ns
History of Thyroid Disease (Interviewer-Administered) (D)	NS	NS	ns	ns
Physical Examination				
Thyroid Gland (D)	NS	ns	NS	ns
Testes (D)	NS	ns	ns	NS
Laboratory				
T ₃ % Uptake (C)	0.010	NS	ns	-0.002
T ₃ % Uptake (D)	NS	NS	ns	ns
TSH (C)	NS	NS	NS	NS
TSH (D)	NS	NS	ns	NS
FSH (C)	NS	NS	NS	ns
FSH ^a (D)	NS	NS	NS	NS
FSH ^b (D)		NS	NS	NS
Testosterone ^c (C)	0.016	+0.005	NS	ns
Testosterone (D)	NS	ns	ns	NS
Fasting Glucose (C)	<0.001	ns	NS	+<0.001
Fasting Glucose (D)	0.001	ns*	NS	+0.002
2-Hour Postprandial Glucose (C)	NS*	-0.049	ns	NS
2-Hour Postprandial Glucose ^d (D)	NS	ns	NS	NS
2-Hour Postprandial Glucose ^e (D)		ns	ns	NS*
Composite Diabetes Indicator (D)	<0.001	ns	NS	+0.001

^aLow FSH contrasted with normal FSH for last three columns.

^bHigh FSH contrasted with normal FSH for last three columns.

^cNegative difference considered adverse for this variable.

^dImpaired contrasted with normal for last three columns.

^eDiabetic contrasted with normal for last three columns.

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.

-: Difference in means negative.

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

NS*/ns*: Marginally significant ($0.05 < p \leq 0.10$).

Note: P-value given if $p \leq 0.05$.

A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis; a capital "NS" in the first column does not imply directionality.

TABLE 15-25. (Continued)
Summary of Categorized Current Dioxin Analyses for
Endocrine Variables
(Ranch Hands and Comparisons)

Variable	All	Adjusted		
		Unknown versus Background	Low versus Background	High versus Background
Questionnaire				
Current Thyroid Function (Self-Administered) (D)	NS	NS	ns	ns
History of Thyroid Disease (Interviewer-Administered) (D)	NS	NS	ns	ns
Physical Examination				
Thyroid Gland (D)	NS	ns	NS	ns
Testes (D)	0.010	ns	ns	+0.001
Laboratory				
T ₃ % Uptake (C)	** (0.005)	** (NS)	** (ns)	** (-0.001)
T ₃ % Uptake (D)	** (NS)	** (NS)	** (ns)	** (ns)
TSH (C)	NS*	NS	NS	+0.010
TSH (D)	NS	NS	ns	NS
FSH (C)	NS	NS	NS	NS
FSH ^a (D)	NS	NS	NS	ns
FSH ^b (D)		NS	NS	NS
Testosterone ^c (C)	NS	NS	NS	ns
Testosterone ^{c,d} (C)	<0.001	+0.001	ns	-0.010
Testosterone (D)	** (NS)	** (ns)	** (ns)	** (NS)
Fasting Glucose (C)	***(<0.001)	*** (ns)	*** (NS)	*** (+<0.001)
Fasting Glucose (D)	<0.001	ns*	NS	+<0.001
2-Hour Postprandial Glucose (C)	NS	ns	ns	NS
2-Hour Postprandial Glucose ^d (C)	0.010	-0.035	ns	+0.041
2-Hour Postprandial Glucose ^e (D)	NS	NS	NS	NS
2-Hour Postprandial Glucose ^f (D)		ns	ns	+0.035
Composite Diabetes Indicator (D)	** (0.003)	** (ns)	** (NS)	** (+<0.001)

^aLow FSH contrasted with normal FSH for last three columns.

^bHigh FSH contrasted with normal FSH for last three columns.

^cNegative difference considered adverse for this variable.

^dAdjusted results from models without percent body fat presented for this variable; see Appendix Table N-2 for a detailed description of these analyses.

^eImpaired contrasted with normal for last three columns.

^fDiabetic contrasted with normal for last three columns.

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.

-: Difference in means negative.

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

NS*/ns* Marginally significant ($0.05 < p \leq 0.10$).

** (NS)/** (ns): Categorized current dioxin-by-covariate interaction ($p \leq 0.05$); not significant when interaction is deleted; refer to Appendix Table N-1 for a detailed description of this interaction.

** (...): Categorized current dioxin-by-covariate interaction ($p \leq 0.05$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table N-1 for a detailed description of this interaction.

TABLE 15-25. (Continued)
Summary of Categorized Current Dioxin Analyses for
Endocrine Variables
(Ranch Hands and Comparisons)

*** (NS)/*** (ns): Categorized current dioxin-by-covariate interaction ($p \leq 0.01$); not significant when interaction is deleted; refer to Table I-1 for a detailed description of this interaction.

*** (...): Categorized current dioxin-by-covariate interaction ($p \leq 0.01$); significant when interaction is deleted and p-value is given in parentheses; refer to Table I-1 for a detailed description of this interaction.

Note: P-value given if $p \leq 0.05$.

Appendix Table N-2 contains detailed analyses for models without percent body fat.

A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis; a capital "NS" in the first column does not imply directionality.

assumptions. The adjusted relative risk was marginally significant for Ranch Hands with an early tour under the maximal assumption. The adjusted analyses of categorized current dioxin found that Ranch Hands in the high current dioxin category were 3.8 times more likely to have an abnormal testes than Comparisons in the background category.

Laboratory Examination Variables

Seven laboratory examination variables were analyzed to assess current endocrine function: T₃ % uptake, TSH, FSH, testosterone, fasting glucose, 2-hour postprandial glucose, and a composite diabetes indicator. Each variable was analyzed in continuous and discrete forms, except for the composite diabetes indicator, which was only analyzed discretely.

Model 1: Ranch Hands – Initial Dioxin

Adjusted analyses found that initial dioxin was significantly associated with increases in diabetes, fasting glucose, and 2-hour postprandial glucose; significant decreases were noted in T₃ % uptake and testosterone. Under both the minimal and maximal assumptions, the adjusted initial dioxin analyses found a significant negative relationship with T₃ % uptake in its continuous form. The analyses of discretized T₃ % uptake were not significant. No significant findings were noted for either the unadjusted or adjusted initial dioxin analyses of TSH and FSH.

For the continuous analysis of testosterone, the interaction of initial dioxin and personality type was significant under both assumptions. Stratifying by personality type, a significant negative association was seen between testosterone and initial dioxin for type A Ranch Hands. This contrasted with a nonsignificant positive association for type B Ranch Hands. Excluding the interaction, contrary results arose based on which covariates were used for adjustment. No significant results were found for the maximal analysis when adjusting for percent body fat, age, and race, but a highly significant negative association was found when percent body fat was deleted from the model. The minimal analysis displayed similar results. Despite these findings, the prevalence of abnormally low testosterone levels was not significantly associated with initial dioxin for any of the analyses of discretized testosterone.

The longitudinal analyses found that Ranch Hands with higher levels of initial dioxin had less of a decrease in testosterone between 1982 and 1987 than Ranch Hands with lower levels of initial dioxin. These results are inconsistent with the previously discussed findings, which showed that higher levels of dioxin were associated significantly with lower levels of testosterone, when percent body fat was not in the adjusted model.

The unadjusted initial dioxin analysis of 2-hour postprandial glucose in its continuous form was not significant under the minimal assumption, but the maximal analysis revealed a significant positive association. The adjusted minimal analysis detected a significant interaction between initial dioxin and percent body fat, but stratified results did not show a significant initial dioxin effect for either normal/lean Ranch Hands or for obese Ranch Hands. Ignoring the interaction, adjusted results for both assumptions were not significant when percent body fat was retained in the final model. However, comparable to the testosterone findings, the association between initial dioxin and 2-hour postprandial glucose became significant when percent body fat was removed from the model.

Under both assumptions, the overall initial dioxin effect was not significant for either the unadjusted analysis of discretized 2-hour postprandial glucose or for the adjusted analysis that kept percent body fat in the model. However, these analyses indicated a marginally significant increased risk of diabetic glucose levels for Ranch Hands in the high initial dioxin category relative to the low category. This contrast became significant when percent body fat was deleted from the adjusted model. The overall dioxin effect was of borderline significance in the adjusted model without percent body fat.

All unadjusted and adjusted initial dioxin analyses for fasting glucose and for the composite diabetes indicator were significant.

Model 2: Ranch Hands – Current Dioxin and Time

The association between current dioxin and the laboratory variables did not differ significantly between time since tour strata for most analyses. Under the minimal assumption, the current dioxin-by-time interaction was not significant for all analyses, except for the adjusted analysis of T₃ % uptake treated as a continuous variable (marginally significant results were noted for the unadjusted analysis of T₃ % uptake and for the unadjusted and adjusted continuous analyses of FSH and fasting glucose). For T₃ % uptake, the association with current dioxin was significantly negative for Ranch Hands with more than 18.6 years since tour, but a nonsignificant positive association was seen for Ranch Hands with time since tour of 18.6 years or less.

Under the maximal assumption, the interaction between current dioxin and time was not significant for all variables except for the analyses of FSH. Under the maximal assumption, higher levels of FSH were associated significantly with dioxin among Ranch Hands with a later time since tour. The association between FSH and dioxin was not significant and negative for Ranch hands with an early tour.

However, the adjusted maximal analyses detected significant positive associations between current levels of dioxin and fasting glucose within each time stratum. In addition, the continuous analyses of 2-hour postprandial glucose found a marginally significant positive association with dioxin for Ranch Hands with an early tour; the association became significant when percent body fat was excluded from the adjusted model (adjusted for age and personality type). The discrete analyses of 2-hour postprandial glucose were significant or marginally significant for Ranch Hands with a later tour. Ranch Hands with a later tour in the high current dioxin category had an increase in diabetic glucose levels relative to those in the low current dioxin category. This finding was marginally significant under the minimal assumption and significant under the maximal assumption.

Under both the minimal and maximal assumptions, there was a significant or marginally significant increased risk of diabetes associated with current dioxin levels within each time stratum. However, there was no significant interaction between current dioxin and time.

The adjusted analyses detected significant current dioxin-by-time-by-personality type interactions for TSH and for 2-hour postprandial glucose, but stratified results did not indicate

a dioxin effect for either variable. There was no significant current dioxin-by-time interaction in the longitudinal analyses of T₃ % uptake, TSH, and testosterone.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The adjusted analyses of categorized current dioxin found that Ranch Hands in the high current dioxin category (>33.3 ppt) had significantly higher incidences of diabetes and abnormally high levels of fasting glucose relative to the background category. Adjusted analyses also found that these Ranch Hands had significantly higher mean levels of TSH, fasting glucose, and 2-hour postprandial glucose than the background category, and significantly lower mean levels of T₃ % uptake and testosterone. For all laboratory variables, Ranch Hands in the low current dioxin category (15 ppt to 33.3 ppt) never differed significantly from the background group (exclusive of interaction analyses). The unknown versus background contrast was often in the opposite direction of the high versus background contrast. Ranch Hands in the unknown current dioxin category (0 ppt to 10 ppt) had a significantly higher mean level of testosterone and a significantly lower mean postprandial glucose level than the background group.

For T₃ % uptake in its continuous form, the unadjusted and adjusted analyses found a significant overall difference among current dioxin categories, with the mean T₃ % uptake for the high current dioxin category significantly less than the background mean. The interaction between current dioxin and age was significant for both the continuous and discrete adjusted analyses of T₃ % uptake. The interaction for the continuous analysis occurred partly because the difference in mean T₃ % uptake for the low versus background contrast was significantly negative for participants born in or after 1942, but it was marginally positive for individuals born before 1942. This same pattern was seen for the discrete analysis, but neither age-specific contrast was significant.

The mean TSH for the high current dioxin category was significantly greater than the background mean in the adjusted analysis.

The mean testosterone for Ranch Hands in the high current dioxin category was significantly less than the background mean, and the mean for the unknown category was significantly more than the background mean, adjusting for the age-by-race interaction. However, when percent body fat was included in the model, neither of these findings was significant. The unadjusted analysis of discretized testosterone found relatively more abnormally low testosterone levels in the high category than in the other three current dioxin categories, but no significant contrasts were noted. The adjusted analysis for discretized testosterone revealed a significant interaction between personality type and current dioxin. Stratified results showed a significant increased risk of an abnormally low testosterone level for the high current dioxin category relative to the background category for type A participants.

In the adjusted analyses of fasting glucose, there was a significant interaction between categorized current dioxin and lifetime alcohol history for older Ranch Hands. Stratified results showed that the mean difference between the high current dioxin category and the background category increased with levels of lifetime alcohol consumption.

Adjusted for age and personality type, the mean 2-hour postprandial glucose was significantly greater in the high current dioxin category than in the background category. Also, the mean for the unknown category was significantly less than the background mean. Comparable to the testosterone findings, neither of these results was significant when percent body fat was retained in the final model. The adjusted analyses of discretized 2-hour postprandial glucose found a significant increased risk of diabetic glucose levels for Ranch Hands in the high category relative to the background category.

The unadjusted and adjusted analyses for the composite diabetes indicator detected a highly significant increased risk of diabetes for Ranch Hands in the high current dioxin category relative to the background category. The adjusted analyses also detected a significant interaction between categorized current dioxin and age. Older Ranch Hands, those born before 1942, were more than three times as likely to be diabetic than similar-aged Comparisons in the background group. This difference was highly significant. In contrast, younger Ranch Hands were only 1.5 times as likely to be considered diabetic than background Comparisons born in or after 1942, which was not significant. No increase in risk was evident for Ranch Hands in the unknown or low categories.

The longitudinal analyses did not indicate that dioxin was associated with changes in T₃ % uptake, TSH, and testosterone.

CONCLUSION

The endocrine assessment found a strong association between initial dioxin and an increase in the incidence of diabetes and the prevalence of testes abnormalities. However, the analyses of current dioxin levels in Ranch Hands and Comparisons indicated that the increased risk was only apparent for Ranch Hands in the high current dioxin category (>33.3 ppt, n=187). These Ranch Hands also had significantly higher mean levels of TSH, fasting glucose, and 2-hour postprandial glucose than background Comparisons, as well as lower mean levels of T₃ % uptake and testosterone. The discrete analyses of these variables found a significant increase in the prevalences of abnormally elevated fasting glucose levels and diabetic 2-hour postprandial glucose levels. The longitudinal analyses provided no consistent support that changes in T₃ % uptake, TSH, and testosterone between 1982 and 1987 were related to dioxin exposure.

These results must be interpreted with caution. Though the data clearly establish a strong association between glucose intolerance and dioxin exposure, it would be premature to draw conclusions regarding cause and effect. Clinically, obesity is well recognized as the most common cause of adult-onset diabetes mellitus. Data analyzed in Chapter 6 document a strong correlation between serum dioxin levels and percent body fat. Pending further investigation into the pharmacokinetics of dioxin in lean versus obese individuals, a causal relationship between exposure to dioxin and diabetes remains to be proven.

CHAPTER 15

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