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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-tetrachloro-dibenzo-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 [T_4] and triiodothyronine [T_3]) 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 hypothalmus. 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 adenohypophysis (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 T_3 % uptake, TSH (μIU/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 T_3 % 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 μIU, 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. T_3 % 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 T_3 % 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 (≤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 T_3 % 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: T_3 % 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) Minimal	Assumption (Ranch Hands Only) Maximal	Categorized Current Dioxin Ranch Hand	Categorized Current Dioxin 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_sAg	EXC	3	4	7	4
Temperature ≥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 – Log_2 (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 – Log_2 (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 – Log_2 (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 – Log_2 (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 - Log_2 (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 - Log_2 (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)

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

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

TABLE 15-3. (Continued)

Analysis of Current Thyroid Function (Self-Administered)

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.437[b]
(n=519)	≤18.6	4.2 (72)	4.7 (128)	1.9 (54)	0.73 (0.37,1.46)	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						0.933[b]
(n=739)	≤18.6	3.8 (106)	4.2 (191)	3.6 (83)	0.89 (0.57,1.39)	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 - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.437[b]	AGE (p=0.459)
(n=519)	≤18.6	0.76 (0.37,1.54)	0.447[c]	RACE (p=0.135)
	>18.6	1.07 (0.62,1.85)	0.813[c]	
h) Maximal			0.960[b]	AGE (p=0.608)
(n=739)	≤18.6	0.91 (0.58,1.42)	0.669[c]	RACE (p=0.086)
	>18.6	0.89 (0.59,1.34)	0.588[c]	

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

TABLE 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 - Log_2 (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 - Log_2 (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)

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

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

TABLE 15-4. (Continued)

Analysis of History of Thyroid Disease (Interviewer-Administered)

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

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=517)						0.347[b]
	≤18.6	2.8 (72)	3.9 (127)	0.0 (54)	0.79 (0.36,1.73)	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)						0.882[b]
	≤18.6	0.9 (106)	3.7 (190)	2.4 (83)	0.97 (0.58,1.62)	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 - Log_2 (Current Dioxin) and Time - Adjusted

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

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

TABLE 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 ≤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.

Physical Examination Variables

Thyroid Gland

Model 1: Ranch Hands – Log_2 (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 – Log_2 (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 – Log_2 (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 – Log_2 (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 - Log_2 (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 - Log_2 (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)

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

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

TABLE 15-5. (Continued)

Analysis of Thyroid Gland

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.887[b]
(n=517)	≤18.6	23.6 (72)	28.9 (128)	18.9 (53)	0.94 (0.72,1.24)	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						0.754[b]
(n=734)	≤18.6	19.8 (106)	28.8 (191)	22.0 (82)	1.01 (0.84,1.22)	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 - Log_2 (Current Dioxin) and Time - Adjusted

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

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

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

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

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

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

TABLE 15-6.

Analysis of Testes

Ranch Hands - Log_2 (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 - Log_2 (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)

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

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

TABLE 15-6. (Continued)

Analysis of Testes

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

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.303[b]
(n=516)	≤18.6	1.4 (71)	4.7 (127)	1.9 (54)	1.49 (0.82,2.68)	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						0.536[b]
(n=736)	≤18.6	1.9 (105)	1.6 (189)	7.2 (83)	1.33 (0.86,2.07)	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 - Log_2 (Current Dioxin) and Time - Adjusted

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

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

TABLE 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)
Unknown	343	Unknown vs. Background	0.75 (0.33,1.69)	0.486	%BFAT (p=0.010)
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 ≤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.

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

T_3 % Uptake (Continuous)

Model 1: Ranch Hands – Log_2 (Initial Dioxin)

T_3 % 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 T_3 % 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 – Log_2 (Current Dioxin) and Time

The association of current dioxin and T_3 % 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 T_3 % 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 T_3 % 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 T_3 % uptake decreased for individuals whose time since tour was more than 18.6 years (minimal:

TABLE 15-7.

Analysis of T_3 % Uptake (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

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

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

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

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm T_3 % uptake versus log_2 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 T_3 % Uptake (Continuous)

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

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

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

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

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm T_3 % uptake versus log_2 dioxin.

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

[d]Test 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 T_3 % Uptake
(Continued)

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)			

[a]Transformed from natural logarithm scale.

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

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

***Categorized current dioxin-by-covariate interaction ($p \leq 0.01$); 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 T_3 % 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 T_3 % 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 T_3 % 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 T_3 % uptake was significant (Table 15-7 [j]: p=0.005) and the mean T_3 % uptake for the high current dioxin category was significantly less than the background mean (p=0.001).

T_3 % Uptake (Discrete)

Model 1: Ranch Hands – Log_2 (Initial Dioxin)

Neither the unadjusted minimal nor the maximal analysis detected a significant association between abnormally high levels of T_3 % uptake and initial dioxin (Table 15-8 [a] and [b]: p=0.240 and p=0.158, respectively). The percentage of abnormally high T_3 % 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 T_3 % uptake treated as a continuous variable, which found a significant decreasing trend between T_3 % 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 T_3 % uptake for

TABLE 15-8.

Analysis of T_3 % Uptake (Discrete)

Ranch Hands - Log_2 (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 - Log_2 (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	- -

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

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

TABLE 15-8. (Continued)

Analysis of T_3 % Uptake
(Discrete)

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

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.777[b]
(n=512)	≤18.6	5.6 (71)	4.0 (126)	1.9 (53)	0.86 (0.46,1.63)	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						0.477[b]
(n=728)	≤18.6	2.8 (106)	5.8 (189)	2.5 (81)	0.91 (0.60,1.39)	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 - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.718[b]	RACE (p=0.088)
(n=512)	≤18.6	0.92 (0.48,1.74)	0.788[c]	
	>18.6	0.76 (0.35,1.66)	0.492[c]	
h) Maximal			0.477[b]	--
(n=728)	≤18.6	0.91 (0.60,1.39)	0.669[c]	
	>18.6	0.72 (0.43,1.20)	0.205[c]	

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

TABLE 15-8. (Continued)

Analysis of T_3 % 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 ($0.01<p\leq0.05$); 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.

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

Model 2: Ranch Hands – Log_2 (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 T_3 % 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 T_3 % uptake (Table 15-8 [i]: p=0.359). Of the four current dioxin categories, the percentage of abnormally high T_3 % 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 – Log_2 (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 – Log_2 (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 μIU/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 μIU/ml versus 0.920 μIU/ml, p=0.010).

TABLE 15-9.

Analysis of TSH (μIU/ml) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	112	1.007	-0.0157 (0.0315)	0.618
(n=431)	Medium	209	1.037		
(R^2<0.001)	High	110	0.995		
b) Maximal	Low	150	1.045	-0.0136 (0.0233)	0.560
(n=608)	Medium	301	1.015		
(R^2<0.001)	High	157	1.013		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean[a]	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
c) Minimal	Low	112	0.910	-0.0070 (0.0322)	0.827	AGE (p=0.026)
(n=431)	Medium	209	0.939			RACE (p=0.021)
(R^2=0.028)	High	110	0.911			
d) Maximal	Low	143	1.039	0.0035 (0.0241)	0.886	AGE (p=0.002)
(n=588)	Medium	291	1.009			PERS (p=0.092)
(R^2=0.021)	High	154	1.043			

[a]Transformed from natural logarithm (X - 0.4) scale (only values above the detection limit of 0.4 used).

[b]Slope and standard error based on natural logarithm (TSH - 0.4) versus log_2 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 (μIU/ml) (Continuous)

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

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

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

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

[a]Transformed from natural logarithm (X - 0.4) scale (only values above the detection limit of 0.4 used).
[b]Slope and standard error based on natural logarithm TSH versus log_2 dioxin.
[c]Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).
[d]Test 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 (μIU/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)			

[a]Transformed from natural logarithm (X - 0.4) scale (only values above the detection limit of 0.4 used).

[e]Difference 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.

[f]P-value is based on difference of means on natural logarithm (X - 0.4) 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.

TSH (Discrete)

Model 1: Ranch Hands – Log_2 (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 – Log_2 (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 – Log_2 (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 – Log_2 (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≤18.6: p=0.014 and p=0.007 for the

TABLE 15-10.

Analysis of TSH (Discrete)

Ranch Hands - Log_2 (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 - Log_2 (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	--

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

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

TABLE 15-10. (Continued)

Analysis of TSH
(Discrete)

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

Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.520[b]
(n=512)	≤18.6	0.0 (71)	2.4 (126)	1.9 (53)	1.48 (0.65,3.36)	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						0.423[b]
(n=704)	≤18.6	1.9 (106)	0.5 (189)	3.7 (81)	1.23 (0.67,2.24)	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 - Log_2 (Current Dioxin) and Time - Adjusted

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

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); 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: Log_2 (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 ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 15-11.

Analysis of FSH (mIU/ml) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

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

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

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

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm FSH versus log_2 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 - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
e) Minimal (n=521) (R^2=0.016)						0.068[c]
	≤18.6	8.25 (72)	7.49 (128)	6.28 (54)	-0.1058 (0.0429)	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)						0.014[c]
	≤18.6	8.24 (106)	7.87 (191)	6.60 (83)	-0.0819 (0.0305)	0.007[d]
	>18.6	7.56 (79)	8.02 (179)	8.04 (104)	0.0184 (0.0270)	0.495[d]

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

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

[a]Transformed from natural logarithm scale.

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

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

[d]Test 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)			

[a]Transformed from natural logarithm scale.

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

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

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

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 Low	Percent Normal	Percent High	Initial Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
a) Minimal	Low	130	0.0	84.6	15.4	Overall†		0.144
(n=521)	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	Low	349	1.7	84.8	13.5	Overall†		0.765
(n=742)	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	Overall†		0.481	AGE (p=0.005)
(n=521)	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	Overall†		0.982	AGE (p<0.001)
(n=742)	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	

[a]Low FSH contrasted with normal FSH.

[b]High 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 Low	Medium	High	Current Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
e) Minimal						C-by-T[a]		0.685
(n=521)	≤18.6	Low	0.0	2.3	3.7	Overall[†]		0.144
		Normal	86.1	88.3	90.7	M vs. L[b]	- -	- -
		High	13.9	9.4	5.6	H vs. L[b]	- -	- -
			(72)	(128)	(54)	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						C-by-T[a]		0.053
(n=742)	≤18.6	Low	2.0	2.3	3.7	Overall[†]		0.191
		Normal	82.3	88.3	90.7	M vs. L[b]	1.09 (0.24,4.86)	0.910[d]
		High	15.7	9.4	5.6	H vs. L[b]	1.70 (0.31,9.26)	0.538[d]
			(198)	(128)	(54)	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]

[a]Test of significance of current dioxin-by-time interaction.
[b]Low FSH contrasted with normal FSH.
[c]High FSH contrasted with normal FSH.
[d]Test 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		C-by-T[a]		0.710	AGE (p=0.012)
(n=521)	≤18.6	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 vs. L[c]	1.37 (0.48,3.90)	0.558[d]	
h) Maximal		C-by-T[a]		0.047	AGE (p<0.001)
(n=742)	≤18.6	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]	

[a]Test of significance of current dioxin-by-time interaction.
[b]Low FSH contrasted with normal FSH.
[c]High FSH contrasted with normal FSH.
[d]Test 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.

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 – Log_2 (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 – Log_2 (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 - Log_2 (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 - Log_2 (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***			

[a]Transformed from square root scale.

[b]Slope and standard error based on square root testosterone versus log_2 dioxin.

***Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); 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: Log_2 (initial dioxin).