# Air Force Health Study

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


*SAIC Team*

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

*Air Force Team*

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

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

Program Manager: R.W. Ogershok

SCIENCE APPLICATIONS
INTERNATIONAL CORPORATION
8400 Westpark Drive
McLean, VA 22102

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

*In conjunction with*

SCRIPPS CLINIC & RESEARCH FOUNDATION,
LA JOLLA, CA

NATIONAL OPINION RESEARCH CENTER,
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**SERUM DIOXIN ANALYSIS OF 1987 EXAMINATION RESULTS**


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# SERUM DIOXIN ANALYSIS OF 1987 EXAMINATION RESULTS

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TABLE OF CONTENTS

VOLUME III

TABLE OF CONTENTS - REPORT

# CHAPTER 8

# NEUROLOGICAL ASSESSMENT

## INTRODUCTION

### Background

The frequent association of subjective neurological symptoms subsequent to herbicide exposure has driven a great deal of the research into the potential neurotoxicity of dioxin. Studies of industrial accidents have demonstrated that the mixed sensorimotor neuropathy associated with extreme chlorophenol toxicity is reversible and there is no scientific evidence to date for any chronic central or peripheral neurological disease associated with low level 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure. Neurobehavioral endpoints in humans, the subject of intensive investigation in this and other studies of Vietnam veterans, are considered separately in Chapter 9, Psychological Assessment.

Earlier research (1, 2) into the effects of perinatal exposure to 2,4-D and 2,4,5-T on neurobehavioral function in weanling rats has been pursued in more recent studies from the same laboratory (3, 4). These and other studies in mice (5) and rabbits (6) have documented changes in the concentrations of several CNS neurotransmitters in association with 2,4-D-induced neurobehavioral dysfunction. In another series of experiments, the neurobehavioral effects of exposure to an ester of 2,4-D were found to be rapidly reversible and the authors proposed a cellular rather than biochemical basis for the tolerance that developed with repeated injections (7, 8, 9).

To date, there has been very little animal research into neurotoxic effects specific to TCDD. One report documented that the intracerebroventricular administration of TCDD in rats was far more toxic than the subcutaneous route, though specific neurological indices were not examined (10). Another study of endpoints associated with acute lethal doses of TCDD in rats concluded that the neuromuscular effects associated with the "wasting syndrome" were primarily on muscle tissue rather than peripheral nerves (11).

The early literature related to 2,4-D-induced neurotoxicity in humans has been summarized in the most recent report of the Air Force Health Study (AFHS) and will not be reviewed in detail here. In association with TCDD exposure, as with 2,4-D, a host of subjective neurological symptoms has been reported and grouped generically under the diagnosis of "neurasthenia." Numerous studies have been published describing populations exposed to TCDD by occupation (12-17), environmental contamination (18-22), and industrial accidents (23-29).

A recent report on the 1976 explosion in Seveso, Italy (24), described the results of examinations conducted in 1982 to 1983 and included objective data derived from a detailed neurological examination and electrophysiological testing. One hundred fifty-two subjects with chloracne, a reliable marker for high-level dioxin exposure, were compared with controls. An abnormality was detected in only 1 of 13 neurophysiological parameters and none of the exposed subjects was found to have a peripheral neuropathy by World Health Organization criteria. These findings were confirmed in another report as well (28). Similar results were

reported in a study conducted 30 years after a runaway reaction that occurred in a trichlorophenol plant in Nitro, West Virginia, in 1949 (15). By neurological examination and nerve conduction velocity studies, no differences were found in 204 exposed subjects (55% had chloracne) compared with 163 controls.

Point source environmental exposure to TCDD has been the focus of numerous epidemiologic studies some of which have included neurological indices in their protocols (18-22). In 1971, waste byproducts contaminated with TCDD from a chlorophenol manufacturing plant were mixed with oils and widely sprayed for dust control in residential areas of eastern Missouri near St. Louis. Soil concentrations in some areas reached 2,200 parts per billion. Comprehensive medical evaluations of exposed and unexposed cohorts have included detailed neurological examinations and in one report (21), quantitative studies of tactile, vibratory, and thermal sensations. A recent review article summarizes the results of these Missouri dioxin studies (30). To date there has been no clinical evidence for any central or peripheral neurological disease associated with these TCDD exposures. The first study (20) to report tissue levels of dioxin in relation to neurological findings found no correlation between the body burden of dioxin and abnormalities in the peripheral indices of pain and vibratory sensation and deep tendon reflexes.

Several studies of Vietnam veterans have included objective neurological data. In the Baseline examination of the AFHS (31), an increased incidence of abnormal Babinski reflexes was noted in Ranch Hand personnel relative to Comparisons, a finding that was not seen at the 1985 examination (32). In a study of 15 veterans who reported subjective symptoms in association with herbicide exposure, one subject was found to have a bilateral peripheral neuropathy related to alcohol abuse. In all others, nerve conduction velocity studies at five peripheral sites were normal (33).

One large-scale study (34) of American Legion veterans who served in Vietnam found an increased incidence of reported neurobehavioral disorders that suggested an association with herbicide exposure. However, the significance is limited by self-reporting bias, the lack of confirmation by clinical examination or medical record review, and the use of unvalidated exposure assumptions.

In contrast to the American Legion study, the Vietnam experience study conducted by the U.S. Centers for Disease Control (CDC) (35) compared 2,490 Vietnam veterans with 1,972 non-Vietnam veterans. Included in the study protocol were comprehensive neurological examinations, nerve conduction velocity studies, and neurophysiological indices of vibratory, thermal, and auditory sensation. Aside from an increased incidence of combat-related high-frequency hearing loss in a pattern typical of a noise etiology, no neurological abnormalities were noted in association with service in Southeast Asia (SEA).

In summary, animal research and studies of humans exposed to high levels of dioxin leave no doubt that the peripheral nervous system is a target organ for acute TCDD toxicity. Longitudinal studies would seem to indicate that the neurological signs and symptoms attributable to acute exposure resolve over time and are not associated with any long-term sequelae.

More detailed summaries of the pertinent scientific literature for the neurological assessment can be found in the report of the previous analyses of the 1987 examination data (36).

## Summary of Previous Analyses of the 1987 Examination Data

The neurological health of the Ranch Hand group was not substantially different from the Comparison group. Of the six questionnaire variables relating to neurological disease, the only significant finding was that Ranch Hands had a higher incidence of hereditary and degenerative neurological disease, such as benign essential tremor. The statistical results of the group contrasts for 30 physical examination variables relating to cranial nerve function, peripheral nerve status, and CNS coordination processes were generally not significant. Unadjusted analyses disclosed marginally more balance/Romberg sign and coordination abnormalities for Ranch Hands than for Comparisons. Conversely, Ranch Hands had significantly fewer biceps reflex abnormalities than Comparisons. The adjusted analyses revealed a significant group-by-insecticide exposure interaction for the cranial nerve index (excluding neck range of motion). Stratified results showed a relative risk significantly greater than 1 for participants who had never been exposed to insecticides, and a relative risk marginally less than 1 for participants who had been exposed to insecticides. The adjusted analysis for coordination detected differences in the relative risks with occupation and insecticide exposure. Stratified analyses found a significant group difference for enlisted groundcrew who had never been exposed to insecticides. There were no significant differences for the other strata. Further investigation found a significant group difference for enlisted groundcrew after excluding the insecticide interaction, and a significant adjusted group difference overall after excluding both interactions. Ranch Hands had significantly more coordination abnormalities than Comparisons for each analysis. The longitudinal analyses for the cranial nerve index and the CNS index were not significant.

## Parameters of the Neurological Assessment

### *Dependent Variables*

The neurological assessment was primarily based on extensive physical examination data on cranial nerve function, peripheral nerve status, and CNS coordination processes. This information was supplemented by verified histories of neurological diseases.

#### Questionnaire Data

Data on all major health conditions since the date of the last health interview were collected during the 1987 health interview. All affirmative histories were subjected to medical records verification. The verified information was used to update the health status of each study participant. The neurological diseases and disorders were classified into eight International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) categories: inflammatory diseases (ICD codes 32000-32600), hereditary and degenerative diseases (ICD codes 33000-33700), peripheral disorders (ICD codes 35000-35900), disorders of the eye (ICD codes 37800-37956), external otitis (ICD codes 38010-38081), tympanic membrane disorder (ICD codes 38420-38500), hearing loss (ICD codes 38900-38999), and other neurological disorders (ICD codes 34000-34900). There were 389 cases in the ICD-9-CM category of other neurological disorders based on all assayed participants. The disorders in this category included multiple sclerosis (3 Ranch Hands and 1 Comparison), other demyelinating diseases of the central nervous system (2 Ranch Hands

and 1 Comparison), hemiplegia (4 Ranch Hands and 1 Comparison), other paralytic syndromes (9 Ranch Hands and 4 Comparisons), epilepsy (7 Ranch Hands and 1 Comparison), migraine (20 Ranch Hands and 14 Comparisons), catalepsy or narcolepsy (0 Ranch Hands and 1 Comparison), unspecified encephalopathy (157 Ranch Hands and 152 Comparisons), other conditions of the brain (1 Ranch Hand and 4 Comparisons), and other unspecified disorders of the nervous system (5 Ranch Hands and 2 Comparisons). Some participants had conditions in more than one category. The analyses of questionnaire information in the neurological assessment were based on verified data only. Each of the eight variables was coded as yes/no.

Participants with positive serological tests for syphilis and participants with a verified pre-SEA history of these disorders were excluded from all analyses of these neurological variables.

**Physical Examination Data**

During the physical examination, assessments were made of cranial nerve function, peripheral nerve status, and CNS coordination processes.

The evaluation of cranial nerve function was based on the following 17 variables: smell, visual fields, light reaction, ocular movement, facial sensation, corneal reflex, jaw clench, smile, palpebral fissure, balance, gag reflex, speech, tongue position relative to midline, palate and uvula movement, neck range of motion, cranial nerve index, and the index excluding neck range of motion. All of these variables were scored as normal/abnormal except jaw clench, which was scored as symmetric/deviated. Left and right determinations were combined to produce a single normal/abnormal result, where normal indicates that both left and right determinations were normal. The cranial nerve index was created by combining responses for the 15 cranial nerve parameters into a single index, which was classified as normal if all parameters were normal. An index was also created excluding the hypoglossal nerve (neck range of motion). No participants had an abnormal corneal reflex. No assayed participants had an abnormal jaw clench, gag reflex, or tongue position relative to midline. One assayed Comparison, but no Ranch Hands, had a palate and uvula movement abnormality.

Peripheral nerve status was assessed by light pin prick, light touch (cotton sticks), visual inspection of muscle mass (and palpation, if indicated), vibratory sensation as measured at the ankle with a tuning fork of 128 Hz, three deep tendon reflexes (patellar, Achilles, and biceps), and the Babinski reflex. Muscle status was a constructed variable using data on bulk, tone of upper and lower extremities and the strength of distal wrist extensors, ankle/toe flexors, proximal deltoids, and hip flexors. Muscle status was classified as normal if all of the components were normal. The reflexes were coded as normal if they were sluggish, active, or very active; reflexes classified as absent, transient clonus, or sustained clonus were coded as abnormal for the analyses.

The evaluation of CNS coordination processes was based on the analysis of the following variables: tremor, coordination, Romberg sign, gait, and CNS index. For these variables, multiple determinations were combined to form a single result, which was normal if all determinations were normal. Coordination was an index defined as normal if the Romberg

sign, finger-nose-finger and heel-knee-shin coordination processes, rapidly alternating movements of pronation/supination of hands, and rapid patting were normal. The CNS index was based on tremor, coordination, and gait; this index was coded as normal if all three of the components were normal.

Participants with positive serological tests for syphilis were excluded from all analyses of these neurological variables. Participants with contact lenses in place were excluded from the analysis of the corneal reflex (n=19 based on all participants). Participants with peripheral edema were excluded from the analyses of pin prick, light touch, and ankle vibration.

***Covariates***

The neurological assessment analyzed the effects of age, race, lifetime alcohol history, diabetic class, and insecticide exposure in the adjusted statistical analyses. Occupation was included as a covariate for the analyses of other neurological disorders because of a strong association. The lifetime alcohol history covariate was based on self-reported information from the questionnaire. The respondent's average daily alcohol consumption was determined for various drinking stages throughout his lifetime, and an estimate of the corresponding total number of drink-years (1 drink-year is the equivalent of drinking 1.5 ounces of 80-proof alcoholic beverage per day for 1 year) was derived. The exposure to insecticides covariate represents lifetime exposure based on self-reported questionnaire data.

Age and lifetime alcohol history were treated as continuous variables for all adjusted analyses, but they were categorized to explore interactions. Appendix Table G-1 presents the interaction summaries. Insecticide exposure was categorized (yes/no) for all analyses.

***Relation to Baseline, 1985, and 1987 Studies***

With the exception of the ICD-9-CM category of other neurological disorders, otitis, hearing loss, and the neurological summary indices, the variables analyzed for this study were also analyzed in the Baseline and 1985 studies. Other neurological disorders, the cranial nerve indices with and without neck range of motion, and the CNS index were variables added to the analysis of the 1985 examination. Analyses of otitis and hearing loss were included in the previous report of the 1987 examination.

The neurological longitudinal analyses were based on the cranial nerve index and the CNS index from the 1985 and 1987 neurological examinations conducted at the Scripps Clinic and Research Foundation (SCRF). To enhance the comparability, the longitudinal assessment contrasted differences between the 1985 and 1987 examinations.

**Statistical Methods**

The basic statistical analysis methods used in the neurological assessment are described in Chapter 4, Statistical Methods.

Table 8-1 summarizes the statistical analyses performed for the 1987 neurological assessment. The modeling strategy for the adjusted analyses was modified to always include age in the model, regardless of the statistical significance. In general, no covariates other than age were examined in the adjusted analyses of the questionnaire variables

**TABLE 8-1.**

**Statistical Analysis for the Neurological Assessment**

**Dependent Variables**

| Variable | Data Source | Data Form | Cutpoints | Candidate Covariates | Statistical Analyses |
|---|---|---|---|---|---|
| Inflammatory Diseases | Q/PE-V | D | Yes<br>No | -- | U:LR,CS,FT |
| Hereditary and Degenerative Diseases | Q/PE-V | D | Yes<br>No | AGE | U:LR<br>A:LR |
| Peripheral Disorders | Q/PE-V | D | Yes<br>No | AGE | U:LR<br>A:LR |
| Disorders of the Eye | Q/PE-V | D | Yes<br>No | AGE | U:LR<br>A:LR |
| Otitis | Q/PE-V | D | Yes<br>No | AGE | U:LR<br>A:LR |
| Tympanic Membrane Disorders | Q/PE-V | D | Yes<br>No | AGE | U:LR<br>A:LR |
| Hearing Loss | Q/PE-V | D | Yes<br>No | AGE | U:LR<br>A:LR |
| Other Neurological Disorders | Q/PE-V | D | Yes<br>No | AGE,<br>OCC | U:LR<br>A:LR |
| Smell | PE | D | Abnormal<br>Normal | AGE | U:LR,CS,FT<br>A:LR |
| Visual Fields | PE | D | Abnormal<br>Normal | -- | U:CS,FT |
| Light Reaction | PE | D | Abnormal<br>Normal | AGE | U:LR,CS,FT<br>A:LR |
| Ocular Movement | PE | D | Abnormal<br>Normal | AGE | U:LR,CS,FT<br>A:LR |
| Facial Sensation | PE | D | Abnormal<br>Normal | AGE | U:LR,CS,FT<br>A:LR |
| Corneal Reflex | PE | D | Abnormal<br>Normal | -- | -- |

**TABLE 8-1. (Continued)**

**Statistical Analysis for the Neurological Assessment**

**Dependent Variables**

| Variable | Data Source | Data Form | Cutpoints | Candidate Covariates | Statistical Analyses |
|---|---|---|---|---|---|
| Jaw Clench | PE | D | Deviated<br>Symmetric | -- | -- |
| Smile | PE | D | Abnormal<br>Normal | AGE | U:LR<br>A:LR |
| Palpebral Fissure | PE | D | Abnormal<br>Normal | AGE,RACE, DRKYR,INS, DIAB | U:LR<br>A:LR |
| Balance | PE | D | Abnormal<br>Normal | -- | U:LR,CS,FT |
| Gag Reflex | PE | D | Abnormal<br>Normal | -- | -- |
| Speech | PE | D | Abnormal<br>Normal | -- | U:CS,FT |
| Tongue Position Relative to Midline | PE | D | Abnormal<br>Normal | -- | -- |
| Palate and Uvula Movement | PE | D | Abnormal<br>Normal | -- | -- |
| Neck Range of Motion | PE | D | Abnormal<br>Normal | AGE,RACE, DRKYR,INS, DIAB | U:LR<br>A:LR |
| Cranial Nerve Index | PE | D | Abnormal<br>Normal | AGE,RACE, DRKYR,INS, DIAB | U:LR<br>A:LR<br>L:LR |
| Cranial Nerve Index Without Range of Motion | PE | D | Abnormal<br>Normal | AGE,RACE, DRKYR,INS, DIAB | U:LR<br>A:LR |
| Pin Prick | PE | D | Abnormal<br>Normal | AGE,RACE, DRKYR,INS, DIAB | U:LR<br>A:LR |

## TABLE 8-1. (Continued)

### Statistical Analysis for the Neurological Assessment

### Dependent Variables

| Variable | Data Source | Data Form | Cutpoints | Candidate Covariates | Statistical Analyses |
|---|---|---|---|---|---|
| Light Touch | PE | D | Abnormal<br>Normal | AGE,RACE,<br>DRKYR,INS,<br>DIAB | U:LR<br>A:LR |
| Muscle Status | PE | D | Abnormal<br>Normal | AGE,RACE,<br>DRKYR,INS,<br>DIAB | U:LR<br>A:LR |
| Vibration | PE | D | Abnormal<br>Normal | AGE,RACE,<br>DRKYR,INS,<br>DIAB | U:LR<br>A:LR |
| Patellar Reflex | PE | D | Abnormal<br>Normal | AGE,RACE,<br>DRKYR,INS,<br>DIAB | U:LR<br>A:LR |
| Achilles Reflex | PE | D | Abnormal<br>Normal | AGE,RACE,<br>DRKYR,INS,<br>DIAB | U:LR<br>A:LR |
| Biceps Reflex | PE | D | Abnormal<br>Normal | -- | U:CS,FT |
| Babinski Reflex | PE | D | Abnormal<br>Normal | -- | U:LR,CS,FT |
| Tremor | PE | D | Abnormal<br>Normal | AGE,RACE,<br>DRKYR,INS,<br>DIAB | U:LR<br>A:LR |
| Coordination | PE | D | Abnormal<br>Normal | AGE,RACE,<br>DRKYR,INS,<br>DIAB | U:LR<br>A:LR |
| Romberg Sign | PE | D | Abnormal<br>Normal | -- | U:LR,CS,FT |
| Gait | PE | D | Abnormal<br>Normal | AGE,RACE,<br>DRKYR,INS,<br>DIAB | U:LR<br>A:LR |

**TABLE 8-1. (Continued)**

**Statistical Analysis for the Neurological Assessment**

**Dependent Variables**

| Variable | Data Source | Data Form | Cutpoints | Candidate Covariates | Statistical Analyses |
|---|---|---|---|---|---|
| Central Nervous System (CNS) Index | PE | D | Abnormal<br>Normal | AGE,RACE, DRKYR,INS, DIAB | U:LR<br>A:LR<br>L:LR |

**Covariates**

| Variable (Abbreviation) | Data Source | Data Form | Cutpoints |
|---|---|---|---|
| Age (AGE) | MIL | D/C | Born ≥1942<br>Born <1942 |
| Race (RACE) | MIL | D | Black<br>Non-Black |
| Occupation (OCC) | MIL | D | Officer<br>Enlisted Flyer<br>Enlisted Groundcrew |
| Lifetime Alcohol History (DRKYR) (Drink-Years) | Q-SR | D/C | ≤40<br>>40 |
| Insecticide Exposure (INS) | Q-SR | D | Yes<br>No |
| Diabetic Class (DIAB) | LAB/Q/PE-V | D | Diabetic: past history or ≥200 mg/dl glucose<br>Impaired: ≥140-200 mg/dl glucose<br>Normal: <140 mg/dl glucose |

**TABLE 8-1. (Continued)**

**Statistical Analysis for the Neurological Assessment**

**Abbreviations**

| | |
|---|---|
| Data Source: | LAB--1987 SCRF laboratory results<br>MIL--Air Force military records<br>PE--1987 SCRF physical examination<br>Q-SR--NORC questionnaire (self-reported)<br>Q/PE-V--1987 Questionnaire and physical examination (verified) |
| Data Form: | D--Discrete analysis only<br>D/C--Appropriate form of analysis (either discrete or continuous) |
| Statistical Analyses: | U--Unadjusted analyses<br>A--Adjusted analyses<br>L--Longitudinal analyses |
| Statistical Methods: | CS--Chi-square contingency table test<br>FT--Fisher's exact test<br>LR--Logistic regression analysis |

(occupation was also included for the analyses of other neurological disorders). The first part of this table lists the dependent variables analyzed, data source, data form, cutpoints, candidate covariates, and statistical analysis methods. The second part of this table provides a description of candidate covariates examined. Abbreviations are used extensively in the body of the table and are defined in the footnotes. Diabetes exhibited a significant positive association with dioxin (see Chapter 15, Endocrine Assessment). Consequently, clinical endpoints in the neurological assessment may be related to dioxin due to the association between dioxin and diabetes. To investigate this possibility, the dioxin effect was evaluated in the context of two models whenever diabetic class was retained in the final model. The results of the analysis adjusting for diabetic class are discussed and tabled in the body of the chapter. Appendix Table G-2 shows additional results for the final model excluding diabetic class. These followup analyses are only discussed if a meaningful change in the results occurred.

Some participants had missing dependent variable or covariate data. Consequently, these individuals could not be included in all analyses. Table 8-2 summarizes the number of participants with missing data, and the number who were excluded from analyses for medical reasons.

Appendix G-1 contains graphic displays of the neurological variables versus initial dioxin for the minimal and maximal cohorts, and the neurological variables versus current dioxin for Ranch Hands and Comparisons. Appendix G-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.

Three statistical models were used to examine the association between a neurological dependent variable and serum dioxin levels. One model related a dependent variable to each Ranch Hand's initial dioxin value (extrapolated from current dioxin values using a first-order pharmacokinetic model). A second model related a dependent variable to each Ranch Hand's current serum dioxin value and each Ranch Hand's time since tour. 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 neurological 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 (36). All three models were implemented with and without covariate adjustment. Chapter 4 provides a more detailed discussion of the models.

## TABLE 8-2.

## Number of Participants Excluded and With Missing Data for the Neurological Assessment

| Variable | Variable Use | Assumption (Ranch Hands Only) Minimal | Assumption (Ranch Hands Only) Maximal | Categorized Current Dioxin Ranch Hand | Categorized Current Dioxin Comparison |
|---|---|---|---|---|---|
| Visual Fields | DEP | 0 | 0 | 0 | 2 |
| Light Reaction | DEP | 0 | 0 | 0 | 2 |
| Ocular Movement | DEP | 0 | 0 | 0 | 1 |
| Facial Sensation | DEP | 0 | 0 | 0 | 1 |
| Corneal Reflex | DEP | 7 | 8 | 7 | 6 |
| Balance | DEP | 0 | 0 | 0 | 1 |
| Speech | DEP | 0 | 0 | 0 | 1 |
| Cranial Nerve Index | DEP | 8 | 9 | 8 | 11 |
| Cranial Nerve Index Without Range of Motion | DEP | 8 | 9 | 8 | 11 |
| Muscle Status | DEP | 0 | 1 | 1 | 1 |
| Patellar Reflex | DEP | 0 | 0 | 0 | 1 |
| Achilles Reflex | DEP | 1 | 2 | 2 | 0 |
| Coordination | DEP | 0 | 1 | 1 | 1 |
| Romberg Sign | DEP | 0 | 0 | 0 | 1 |
| Gait | DEP | 0 | 1 | 1 | 1 |
| CNS Index | DEP | 0 | 1 | 1 | 1 |
| Lifetime Alcohol History | COV | 6 | 9 | 9 | 2 |
| Diabetic Class | COV | 2 | 2 | 3 | 2 |
| Pre-SEA Inflammatory Diseases | EXC | 0 | 0 | 0 | 5 |
| Pre-SEA Hereditary and Degenerative Diseases | EXC | 0 | 1 | 1 | 0 |
| Pre-SEA Peripheral Disorders | EXC | 0 | 1 | 2 | 3 |
| Pre-SEA Disorders of the Eye | EXC | 1 | 2 | 2 | 1 |
| Pre-SEA Tympanic Membrane Disorder | EXC | 5 | 5 | 6 | 5 |
| Pre-SEA Otitis | EXC | 0 | 0 | 0 | 1 |
| Pre-SEA Hearing Loss | EXC | 2 | 3 | 4 | 8 |
| Pre-SEA Other Neurological Diseases | EXC | 1 | 2 | 2 | 3 |
| Syphilis | EXC | 0 | 1 | 2 | 2 |
| Pitting or Nonpitting Edema | EXC | 9 | 12 | 10 | 14 |

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

## RESULTS

### Exposure Analysis

#### *Questionnaire Variables*

##### Inflammatory Diseases

###### *Model 1: Ranch Hands - $Log_2$ (Initial Dioxin)*

The unadjusted initial dioxin analyses of inflammatory diseases were not significant under both the minimal (Table 8-3 [a]: p=0.761) and maximal (Table 8-3 [b]: p=0.409) assumptions. Under both assumptions, there were only two cases of inflammatory disease. One was in the medium initial dioxin category, the other was in the high category. No adjusted analyses were done because of the sparse number of abnormalities.

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

The interaction between current dioxin and time since tour was not evaluated because only two Ranch Hands had a post-SEA history of inflammatory neurological disease. There was only one case within each time stratum.

###### *Model 3: Ranch Hands and Comparisons by Current Dioxin Category*

The incidence of inflammatory diseases did not differ significantly among current dioxin categories in the unadjusted analysis (Table 8-3 [e]: p=0.616). No adjusted analysis was done because there were only three cases of inflammatory disease (one in each of the background, unknown, and high current dioxin categories, and none in the low category).

##### Hereditary and Degenerative Diseases

###### *Model 1: Ranch Hands - $Log_2$ (Initial Dioxin)*

Under both the minimal and maximal assumptions, initial dioxin was not significantly associated with the incidence of hereditary and degenerative diseases (Table 8-4 [a-d]: p>0.55 for the unadjusted and adjusted analyses). The relative risk was less than 1 in each analysis.

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

The interaction between current dioxin and time since tour was not significant for the minimal and maximal analyses of hereditary and degenerative diseases (Table 8-4 [e-h]: p>0.45 for the unadjusted and adjusted analyses).

###### *Model 3: Ranch Hands and Comparisons by Current Dioxin Category*

The incidence of hereditary and degenerative diseases did not differ significantly among the current dioxin categories in the unadjusted analysis (Table 8-4 [i]: 4.0%, 5.6%, 3.6%, and 3.2% for the background, unknown, low, and high current dioxin categories, p=0.524). The overall contrast was also not significant after adjusting for age (Table 8-4 [j]: p=0.612).

## TABLE 8-3.

### Analysis of Inflammatory Diseases

**Ranch Hands - $Log_2$ (Initial Dioxin) - Unadjusted**

| Assumption | Initial Dioxin | n | Percent Yes | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|
| a) Minimal | Low | 130 | 0.0 | 1.18 (0.41,3.43) | 0.761 |
| (n=521) | Medium | 260 | 0.4 | | |
| | High | 131 | 0.8 | | |
| b) Maximal | Low | 184 | 0.0 | 1.46 (0.62,3.46) | 0.409 |
| (n=741) | Medium | 371 | 0.3 | | |
| | High | 186 | 0.5 | | |

[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 8-3. (Continued)

### Analysis of Inflammatory Diseases

**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.) | p-Value |
|---|---|---|---|---|---|---|
| c) Minimal | | | | | | -- |
| (n=521) | ≤18.6 | 0.0 (72) | 0.0 (128) | 1.9 (54) | -- | -- |
| | >18.6 | 1.7 (58) | 0.0 (132) | 0.0 (77) | -- | -- |
| d) Maximal | | | | | | -- |
| (n=741) | ≤18.6 | 0.0 (106) | 0.0 (191) | 1.2 (83) | -- | -- |
| | >18.6 | 0.0 (78) | 0.6 (179) | 0.0 (104) | -- | -- |

--: 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: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

## TABLE 8-3. (Continued)

## Analysis of Inflammatory Diseases

### e) 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 | 779 | 0.1 | All Categories | | 0.616 |
| Unknown | 343 | 0.3 | Unknown vs. Background | 2.27 (0.14,36.48) | 0.999 |
| Low | 196 | 0.0 | Low vs. Background | -- | 0.999 |
| High | 187 | 0.5 | High vs. Background | 4.18 (0.26,67.18) | 0.700 |
| Total | 1,505 | | | | |

--: Relative risk, confidence interval, and p-value not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

## TABLE 8-4.

## Analysis of Hereditary and Degenerative Diseases

### Ranch Hands - $Log_2$ (Initial Dioxin) - Unadjusted

| Assumption | Initial Dioxin | n | Percent Yes | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|
| a) Minimal (n=521) | Low | 130 | 6.9 | 0.90 (0.62,1.31) | 0.565 |
| | Medium | 260 | 3.1 | | |
| | High | 131 | 3.8 | | |
| b) Maximal (n=740) | Low | 183 | 4.4 | 0.94 (0.72,1.24) | 0.684 |
| | Medium | 371 | 4.3 | | |
| | High | 186 | 3.2 | | |

### Ranch Hands - $Log_2$ (Initial Dioxin) - Adjusted

| Assumption | Adj. Relative Risk (95% C.I.)[a] | p-Value | Covariate Remarks |
|---|---|---|---|
| c) Minimal (n=521) | 0.91 (0.62,1.33) | 0.614 | AGE (p=0.826) |
| d) Maximal (n=740) | 0.96 (0.73,1.27) | 0.781 | AGE (p=0.517) |

[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 8-4. (Continued)

## Analysis of Hereditary and Degenerative Diseases

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

| Assumption | Time (Yrs.) | Percent Yes/(n) Current Dioxin Low | Medium | High | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|---|
| e) Minimal | | | | | | 0.482[b] |
| (n=521) | ≤18.6 | 6.9 (72) | 3.9 (128) | 3.7 (54) | 0.81 (0.45,1.48) | 0.495[c] |
| | >18.6 | 6.9 (58) | 1.5 (132) | 5.2 (77) | 1.07 (0.66,1.73) | 0.790[c] |
| f) Maximal | | | | | | 0.936[b] |
| (n=740) | ≤18.6 | 2.9 (105) | 5.8 (191) | 2.4 (83) | 0.98 (0.65,1.47) | 0.907[c] |
| | >18.6 | 5.1 (78) | 3.4 (179) | 3.9 (104) | 1.00 (0.69,1.45) | 0.991[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 | | | 0.492[b] | AGE (p=0.727) |
| (n=521) | ≤18.6 | 0.83 (0.45,1.54) | 0.561[c] | |
| | >18.6 | 1.09 (0.66,1.78) | 0.736[c] | |
| h) Maximal | | | 0.943[b] | AGE (p=0.442) |
| (n=740) | ≤18.6 | 1.01 (0.66,1.54) | 0.972[c] | |
| | >18.6 | 1.03 (0.70,1.51) | 0.887[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 8-4. (Continued)

## Analysis of Hereditary and Degenerative Diseases

### 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 | 784 | 4.0 | All Categories | | 0.524 |
| Unknown | 342 | 5.6 | Unknown vs. Background | 1.43 (0.80,2.57) | 0.232 |
| Low | 196 | 3.6 | Low vs. Background | 0.90 (0.39,2.07) | 0.804 |
| High | 187 | 3.2 | High vs. Background | 0.81 (0.33,1.96) | 0.633 |
| Total | 1,509 | | | | |

### 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 | 784 | All Categories | | 0.612 | AGE (p=0.169) |
| Unknown | 342 | Unknown vs. Background | 1.41 (0.78,2.53) | 0.254 | |
| Low | 196 | Low vs. Background | 0.90 (0.39,2.09) | 0.813 | |
| High | 187 | High vs. Background | 0.88 (0.36,2.16) | 0.777 | |
| Total | 1,509 | | | | |

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.

**Peripheral Disorders**

***Model 1: Ranch Hands - $Log_2$ (Initial Dioxin)***

In both the unadjusted and adjusted initial dioxin analyses, the relative risk of peripheral disorders was not significant under both the minimal and maximal assumptions (Table 8-5 [a-d]: $p>0.55$ for all analyses).

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

The current dioxin-by-time since tour interaction was not significant for either the minimal or maximal analyses of peripheral disorders (Table 8-5 [e-h]: $p>0.15$ in each unadjusted and adjusted analysis).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The unadjusted categorized current dioxin analysis of peripheral disorders was not significant, but the highest incidence of peripheral disorders was in the high current dioxin category (Table 8-5 [i]: 14.7%, 12.3%, 12.8%, and 16.0% for the background, unknown, low, and high current dioxin categories, $p>0.25$ for each contrast). The overall contrast, as well as the three Ranch Hand versus background contrasts, remained nonsignificant after adjustment for age (Table 8-5 [j]: $p>0.20$ for each contrast).

**Disorders of the Eye**

***Model 1: Ranch Hands - $Log_2$ (Initial Dioxin)***

Under both the minimal and maximal assumptions, the initial dioxin analyses did not show a significant association with the incidence of eye disorders (Table 8-6 [a-d]: $p>0.35$ for the unadjusted and adjusted analyses).

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

The current dioxin and time since tour analyses of eye disorders did not find a significant interaction between current dioxin and time under both the minimal and maximal assumptions (Table 8-6 [e-h]: $p>0.80$ in each unadjusted and adjusted analysis).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The incidence of eye disorders did not differ significantly among the four current dioxin categories in the unadjusted analysis (Table 8-6 [i]: 15.8%, 16.7%, 16.9%, and 17.6% for the background, unknown, low, and high current dioxin categories, $p=0.930$). The overall contrast remained nonsignificant (Table 8-6 [j]: $p=0.801$) after adjustment for age.

**Tympanic Membrane Disorders**

***Model 1: Ranch Hands - $Log_2$ (Initial Dioxin)***

Under both the minimal and maximal assumptions, initial dioxin was not significantly associated with the incidence of tympanic membrane disorders (Table 8-7 [a-d]: $p>0.60$ for the unadjusted and adjusted analyses).

## TABLE 8-5.

## Analysis of Peripheral Disorders

### Ranch Hands - $Log_2$ (Initial Dioxin) - Unadjusted

| Assumption | Initial Dioxin | n | Percent Yes | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|
| a) Minimal (n=521) | Low | 130 | 14.6 | 1.01 (0.83,1.24) | 0.900 |
| | Medium | 260 | 14.2 | | |
| | High | 131 | 13.7 | | |
| b) Maximal (n=740) | Low | 183 | 14.8 | 1.00 (0.86,1.16) | 0.999 |
| | Medium | 371 | 13.7 | | |
| | High | 186 | 15.6 | | |

### Ranch Hands - $Log_2$ (Initial Dioxin) - Adjusted

| Assumption | Adj. Relative Risk (95% C.I.)[a] | p-Value | Covariate Remarks |
|---|---|---|---|
| c) Minimal (n=521) | 1.04 (0.85,1.28) | 0.703 | AGE (p=0.294) |
| d) Maximal (n=740) | 1.05 (0.90,1.22) | 0.564 | AGE (p=0.003) |

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

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

## TABLE 8-5. (Continued)

## Analysis of Peripheral Disorders

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

| Assumption | Time (Yrs.) | Percent Yes/(n) Current Dioxin Low | Medium | High | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|---|
| e) Minimal | | | | | | 0.184[b] |
| (n=521) | ≤18.6 | 12.5 (72) | 16.4 (128) | 7.4 (54) | 0.82 (0.57,1.19) | 0.302[c] |
| | >18.6 | 13.8 (58) | 12.1 (132) | 20.8 (77) | 1.11 (0.86,1.44) | 0.418[c] |
| f) Maximal | | | | | | 0.255[b] |
| (n=740) | ≤18.6 | 15.1 (106) | 13.6 (191) | 13.3 (83) | 0.89 (0.70,1.14) | 0.371[c] |
| | >18.6 | 13.0 (77) | 14.0 (179) | 18.3 (104) | 1.07 (0.88,1.31) | 0.488[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 | | | 0.199[b] | AGE (p=0.363) |
| (n=521) | ≤18.6 | 0.86 (0.59,1.25) | 0.421[c] | |
| | >18.6 | 1.14 (0.88,1.49) | 0.315[c] | |
| h) Maximal | | | 0.263[b] | AGE (p=0.003) |
| (n=740) | ≤18.6 | 0.96 (0.74,1.23) | 0.732[c] | |
| | >18.6 | 1.15 (0.94,1.41) | 0.186[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 8-5. (Continued)

## Analysis of Peripheral Disorders

### 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 | 781 | 14.7 | All Categories | | 0.564 |
| Unknown | 341 | 12.3 | Unknown vs. Background | 0.81 (0.56,1.19) | 0.285 |
| Low | 196 | 12.8 | Low vs. Background | 0.85 (0.53,1.35) | 0.482 |
| High | 187 | 16.0 | High vs. Background | 1.11 (0.71,1.71) | 0.650 |
| Total | 1,505 | | | | |

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

| Current Dioxin Category | n | Contrast | Adj. Relative Risk (95% C.I.) | p-Value | Covariate Remarks |
|---|---|---|---|---|---|
| Background | 781 | All Categories | | 0.236 | AGE ($p<0.001$) |
| Unknown | 341 | Unknown vs. Background | 0.79 (0.54,1.16) | 0.226 | |
| Low | 196 | Low vs. Background | 0.85 (0.53,1.36) | 0.506 | |
| High | 187 | High vs. Background | 1.33 (0.85,2.08) | 0.215 | |
| Total | 1,505 | | | | |

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 8-6.

## Analysis of Disorders of the Eye

### Ranch Hands - $Log_2$ (Initial Dioxin) - Unadjusted

| Assumption | Initial Dioxin | n | Percent Yes | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|
| a) Minimal (n=520) | Low | 130 | 18.5 | 1.05 (0.87,1.26) | 0.602 |
| | Medium | 259 | 17.4 | | |
| | High | 131 | 18.3 | | |
| b) Maximal (n=739) | Low | 183 | 15.3 | 1.05 (0.92,1.21) | 0.475 |
| | Medium | 370 | 17.6 | | |
| | High | 186 | 18.3 | | |

### Ranch Hands - $Log_2$ (Initial Dioxin) - Adjusted

| Assumption | Adj. Relative Risk (95% C.I.)[a] | p-Value | Covariate Remarks |
|---|---|---|---|
| c) Minimal (n=520) | 1.07 (0.89,1.29) | 0.486 | AGE (p=0.419) |
| d) Maximal (n=739) | 1.07 (0.93,1.23) | 0.365 | AGE (p=0.306) |

[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 8-6. (Continued)**

**Analysis of Disorders of the Eye**

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

| Assumption | Time (Yrs.) | Percent Yes/(n) Current Dioxin Low | Medium | High | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|---|
| e) Minimal | | | | | | 0.920[b] |
| (n=520) | ≤18.6 | 20.8 (72) | 16.4 (128) | 22.2 (54) | 1.05 (0.79,1.41) | 0.720[c] |
| | >18.6 | 15.5 (58) | 18.3 (131) | 15.6 (77) | 1.08 (0.84,1.38) | 0.563[c] |
| f) Maximal | | | | | | 0.832[b] |
| (n=739) | ≤18.6 | 16.0 (106) | 18.9 (191) | 20.5 (83) | 1.06 (0.87,1.31) | 0.557[c] |
| | >18.6 | 13.0 (77) | 17.4 (178) | 15.4 (104) | 1.10 (0.90,1.33) | 0.346[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 | | | 0.956[b] | AGE (p=0.301) |
| (n=520) | ≤18.6 | 1.10 (0.81,1.48) | 0.546[c] | |
| | >18.6 | 1.11 (0.86,1.43) | 0.423[c] | |
| h) Maximal | | | 0.844[b] | AGE (p=0.165) |
| (n=739) | ≤18.6 | 1.10 (0.89,1.36) | 0.391[c] | |
| | >18.6 | 1.13 (0.93,1.37) | 0.225[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 8-6. (Continued)

## Analysis of Disorders of the Eye

### 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 | 15.8 | All Categories | | 0.930 |
| Unknown | 342 | 16.7 | Unknown vs. Background | 1.06 (0.75,1.50) | 0.727 |
| Low | 195 | 16.9 | Low vs. Background | 1.08 (0.71,1.65) | 0.712 |
| High | 187 | 17.6 | High vs. Background | 1.14 (0.75,1.74) | 0.546 |
| Total | 1,507 | | | | |

### 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 | | 0.801 | AGE (p=0.011) |
| Unknown | 342 | Unknown vs. Background | 1.05 (0.74,1.48) | 0.798 | |
| Low | 195 | Low vs. Background | 1.09 (0.71,1.66) | 0.699 | |
| High | 187 | High vs. Background | 1.24 (0.81,1.91) | 0.321 | |
| Total | 1,507 | | | | |

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 8-7.

## Analysis of Tympanic Membrane Disorder

### 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=516) | Low | 129 | 5.4 | 0.94 (0.68,1.29) | 0.684 |
| | Medium | 257 | 5.8 | | |
| | High | 130 | 6.2 | | |
| b) Maximal (n=736) | Low | 184 | 3.8 | 1.01 (0.80,1.27) | 0.959 |
| | Medium | 368 | 6.3 | | |
| | High | 184 | 5.4 | | |

### Ranch Hands - $Log_2$ (Initial Dioxin) - Adjusted

| Assumption | Adj. Relative Risk (95% C.I.)[a] | p-Value | Covariate Remarks |
|---|---|---|---|
| c) Minimal (n=516) | 0.99 (0.72,1.37) | 0.950 | AGE (p=0.153) |
| d) Maximal (n=736) | 1.06 (0.84,1.35) | 0.618 | AGE (p=0.023) |

[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 8-7. (Continued)

## Analysis of Tympanic Membrane Disorder

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

| Assumption | Time (Yrs.) | Percent Yes/(n) Current Dioxin Low | Medium | High | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|---|
| e) Minimal | | | | | | 0.435[b] |
| (n=516) | ≤18.6 | 2.8 (72) | 4.0 (125) | 3.7 (54) | 1.07 (0.58,1.97) | 0.821[c] |
| | >18.6 | 8.6 (58) | 8.4 (131) | 6.6 (76) | 0.80 (0.54,1.19) | 0.270[c] |
| f) Maximal | | | | | | 0.844[b] |
| (n=736) | ≤18.6 | 3.8 (106) | 3.7 (189) | 3.7 (82) | 0.98 (0.63,1.51) | 0.922[c] |
| | >18.6 | 6.4 (78) | 8.4 (178) | 5.8 (103) | 0.93 (0.69,1.24) | 0.616[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 | | | 0.419[b] | AGE (p=0.347) |
| (n=516) | ≤18.6 | 1.14 (0.61,2.11) | 0.681[c] | |
| | >18.6 | 0.84 (0.56,1.26) | 0.406[c] | |
| h) Maximal | | | 0.817[b] | AGE (p=0.066) |
| (n=736) | ≤18.6 | 1.05 (0.67,1.65) | 0.830[c] | |
| | >18.6 | 0.99 (0.73,1.33) | 0.929[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 8-7. (Continued)

## Analysis of Tympanic Membrane Disorder

### 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 | 779 | 4.1 | All Categories | | 0.375 |
| Unknown | 342 | 3.5 | Unknown vs. Background | 0.85 (0.43,1.67) | 0.635 |
| Low | 193 | 6.7 | Low vs. Background | 1.69 (0.87,3.28) | 0.124 |
| High | 185 | 4.9 | High vs. Background | 1.19 (0.56,2.55) | 0.647 |
| 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 | 779 | All Categories | | 0.315 | AGE (p=0.087) |
| Unknown | 342 | Unknown vs. Background | 0.83 (0.42,1.64) | 0.600 | |
| Low | 193 | Low vs. Background | 1.70 (0.87,3.31) | 0.116 | |
| High | 185 | High vs. Background | 1.33 (0.62,2.87) | 0.470 | |
| 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.

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

The unadjusted and adjusted current dioxin and time since tour analyses of tympanic membrane disorders did not find a significant current dioxin-by-time interaction under either the minimal or maximal assumption (Table 8-7 [e-h]: $p>0.40$ in each analysis).

*Model 3: Ranch Hands and Comparisons by Current Dioxin Category*

The overall contrast was not significant in both the unadjusted and adjusted categorized current dioxin analysis of tympanic membrane disorders (Table 8-7 [i] and [j]: $p=0.375$ and $p=0.315$, respectively). The highest incidence was in the low current dioxin category (4.1%, 3.5%, 6.7%, and 4.9% for the background, unknown, low, and high current dioxin categories).

**Otitis**

*Model 1: Ranch Hands - $Log_2$ (Initial Dioxin)*

Under both the minimal and maximal assumptions, the initial dioxin analyses did not find a significant risk of otitis (Table 8-8 [a-d]: $p>0.20$ for the unadjusted and adjusted analyses).

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

Under the minimal assumption, the unadjusted current dioxin and time since tour analysis of otitis did not show a significant current dioxin-by-time interaction (Table 8-8 [e]: $p=0.791$), but a significant interaction was found under the maximal assumption (Table 8-8 [f]: $p=0.032$). In the maximal cohort, the estimated relative risk of otitis was significantly less than 1 for Ranch Hands with a later tour (time$\leq$18.6: Est. RR=0.62, $p=0.012$). In this stratum, the incidence of otitis decreased with current levels of dioxin (14.2%, 7.3%, and 3.6% for the low, medium, and high current dioxin categories). The estimated relative risk was less than 1, but not significant, for Ranch Hands in the maximal cohort with an early tour (time>18.6: Est. RR=0.97, $p=0.760$).

Similar results were noted after adjusting for age. The current dioxin-by-time interaction was not significant under the minimal assumption (Table 8-8 [g]: $p=0.852$), and it remained significant under the maximal assumption (Table 8-8 [h]: $p=0.031$). The adjusted relative risk was significantly less than 1 for Ranch Hands with a later tour (time$\leq$18.6: Adj. RR=0.64, $p=0.020$).

*Model 3: Ranch Hands and Comparisons by Current Dioxin Category*

The incidence of otitis did not differ significantly among the current dioxin categories in the unadjusted analysis (Table 8-8 [i]: 12.4%, 14.0%, 12.8%, and 8.6% for the background, unknown, low, and high current dioxin categories, $p=0.308$). The overall contrast remained nonsignificant after adjusting for age (Table 8-8 [j]: $p=0.633$).

**Hearing Loss**

*Model 1: Ranch Hands - $Log_2$ (Initial Dioxin)*

Neither the unadjusted minimal nor maximal analyses of hearing loss showed a significant association with initial dioxin (Table 8-9 [a] and [b]: $p=0.504$ for the minimal

## TABLE 8-8.

## Analysis of Otitis

### Ranch Hands - $Log_2$ (Initial Dioxin) - Unadjusted

| Assumption | Initial Dioxin | n | Percent Yes | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|
| a) Minimal (n=521) | Low | 130 | 8.5 | 1.04 (0.82,1.31) | 0.761 |
| | Medium | 260 | 10.4 | | |
| | High | 131 | 10.7 | | |
| b) Maximal (n=741) | Low | 184 | 15.2 | 0.90 (0.76,1.08) | 0.246 |
| | Medium | 371 | 10.8 | | |
| | High | 186 | 8.6 | | |

### Ranch Hands - $Log_2$ (Initial Dioxin) - Adjusted

| Assumption | Adj. Relative Risk (95% C.I.)[a] | p-Value | Covariate Remarks |
|---|---|---|---|
| c) Minimal (n=521) | 1.13 (0.89,1.43) | 0.331 | AGE (p=0.004) |
| d) Maximal (n=741) | 0.93 (0.78,1.12) | 0.451 | AGE (p=0.038) |

[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 8-8. (Continued)

### Analysis of Otitis

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

| Assumption | Time (Yrs.) | Percent Yes/(n) Current Dioxin Low | Medium | High | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|---|
| e) Minimal | | | | | | 0.791[b] |
| (n=521) | ≤18.6 | 2.8 (72) | 7.0 (128) | 3.7 (54) | 0.86 (0.49,1.51) | 0.601[c] |
| | >18.6 | 13.8 (58) | 15.9 (132) | 13.0 (77) | 0.94 (0.71,1.23) | 0.642[c] |
| f) Maximal | | | | | | 0.032[b] |
| (n=741) | ≤18.6 | 14.2 (106) | 7.3 (191) | 3.6 (83) | 0.62 (0.42,0.90) | 0.012[c] |
| | >18.6 | 14.1 (78) | 15.6 (179) | 12.5 (104) | 0.97 (0.79,1.19) | 0.760[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 | | | 0.852[b] | AGE (p=0.032) |
| (n=521) | ≤18.6 | 0.96 (0.54,1.69) | 0.886[c] | |
| | >18.6 | 1.02 (0.76,1.35) | 0.905[c] | |
| h) Maximal | | | 0.031[b] | AGE (p=0.140) |
| (n=741) | ≤18.6 | 0.64 (0.43,0.93) | 0.020[c] | |
| | >18.6 | 1.00 (0.81,1.24) | 0.973[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 8-8. (Continued)

## Analysis of Otitis

### 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 | 12.4 | All Categories | | 0.308 |
| Unknown | 343 | 14.0 | Unknown vs. Background | 1.15 (0.79,1.67) | 0.459 |
| Low | 196 | 12.8 | Low vs. Background | 1.03 (0.65,1.66) | 0.889 |
| High | 187 | 8.6 | High vs. Background | 0.66 (0.38,1.15) | 0.145 |
| Total | 1,509 | | | | |

### 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 | | 0.633 | AGE (p<0.001) |
| Unknown | 343 | Unknown vs. Background | 1.13 (0.78,1.64) | 0.532 | |
| Low | 196 | Low vs. Background | 1.04 (0.65,1.67) | 0.863 | |
| High | 187 | High vs. Background | 0.76 (0.43,1.34) | 0.343 | |
| Total | 1,509 | | | | |

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 8-9.

## Analysis of Hearing Loss

### 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=519) | Low | 130 | 73.9 | 0.95 (0.81,1.11) | 0.504 |
| | Medium | 259 | 71.4 | | |
| | High | 130 | 70.0 | | |
| b) Maximal (n=738) | Low | 183 | 73.8 | 0.94 (0.84,1.06) | 0.344 |
| | Medium | 370 | 74.6 | | |
| | High | 185 | 68.1 | | |

### Ranch Hands - $Log_2$ (Initial Dioxin) - Adjusted

| Assumption | Adj. Relative Risk (95% C.I.)[a] | p-Value | Covariate Remarks |
|---|---|---|---|
| c) Minimal (n=519) | 1.16 (0.97,1.39) | 0.100 | AGE (p<0.001) |
| d) Maximal (n=738) | 1.08 (0.95,1.22) | 0.257 | AGE (p<0.001) |

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

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

## TABLE 8-9. (Continued)

## Analysis of Hearing Loss

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

| Assumption | Time (Yrs.) | Percent Yes/(n) Current Dioxin Low | Medium | High | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|---|
| e) Minimal | | | | | | 0.555[b] |
| (n=519) | ≤18.6 | 70.8 (72) | 70.3 (128) | 64.2 (53) | 0.84 (0.66,1.08) | 0.182[c] |
| | >18.6 | 79.3 (58) | 72.5 (131) | 72.7 (77) | 0.93 (0.75,1.15) | 0.517[c] |
| f) Maximal | | | | | | 0.674[b] |
| (n=738) | ≤18.6 | 68.9 (106) | 72.6 (190) | 62.2 (82) | 0.91 (0.77,1.09) | 0.319[c] |
| | >18.6 | 84.6 (78) | 76.4 (178) | 70.2 (104) | 0.87 (0.74,1.02) | 0.095[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 | | | 0.748[b] | AGE (p<0.001) |
| (n=519) | ≤18.6 | 1.14 (0.87,1.51) | 0.347[c] | |
| | >18.6 | 1.21 (0.95,1.55) | 0.125[c] | |
| h) Maximal | | | 0.690[b] | AGE (p<0.001) |
| (n=738) | ≤18.6 | 1.09 (0.91,1.32) | 0.345[c] | |
| | >18.6 | 1.04 (0.87,1.24) | 0.674[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 8-9. (Continued)

## Analysis of Hearing Loss

### 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 | 776 | 76.0 | All Categories | | 0.082 |
| Unknown | 341 | 75.1 | Unknown vs. Background | 0.95 (0.71,1.28) | 0.731 |
| Low | 195 | 74.9 | Low vs. Background | 0.94 (0.65,1.35) | 0.736 |
| High | 186 | 66.7 | High vs. Background | 0.63 (0.45,0.89) | 0.009 |
| Total | 1,498 | | | | |

### 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 | 776 | All Categories | | 0.660 | AGE (p<0.001) |
| Unknown | 341 | Unknown vs. Background | 0.82 (0.60,1.12) | 0.211 | |
| Low | 195 | Low vs. Background | 0.95 (0.64,1.40) | 0.787 | |
| High | 186 | High vs. Background | 0.91 (0.63,1.31) | 0.600 | |
| Total | 1,498 | | | | |

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.

analysis and p=0.344 for the maximal analysis). After adjustment for age, the relative risk under the minimal assumption became marginally more than 1 (Table 8-9 [c]: Adj. RR=1.16, p=0.100), although the unadjusted incidence of hearing loss decreased with levels of initial dioxin (73.9%, 71.4%, and 70.0% for the low, medium, and high initial dioxin categories in the minimal cohort). Ranch Hands in the high initial dioxin category were on the average 4.8 years younger than those in the low category. The adjusted maximal analysis did not find a significant increased risk of hearing loss (Table 8-9 [d]: p=0.257).

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

Under both the minimal and maximal assumptions, the interaction between current dioxin and time since tour was not significant for the analyses of hearing loss (Table 8-9 [e-h]: p>0.55 in each of the unadjusted and adjusted analysis).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The incidence of hearing loss differed marginally among the current dioxin categories in the unadjusted analysis (Table 8-9 [i]: 76.0%, 75.1%, 74.9%, and 66.7% for the background, unknown, low, and high current dioxin categories, p=0.082). Relative to the background category, there was a significant decreased risk of hearing loss for Ranch Hands in the high current dioxin category (Est. RR=0.63, 95% C.I.: [0.45,0.89], p=0.009). However, this occurred because Ranch Hands in the high current dioxin category were on the average younger than Comparisons in the background category (63% of of Ranch Hands in the high category were born in or after 1942 versus 41% of Comparisons in the background category). For this reason, the overall contrast and the high versus background contrast became nonsignificant after adjustment for age (Table 8-9 [j]: p=0.660 and p=0.600, respectively).

**Other Neurological Disorders**

Preliminary screening analyses showed that occupation was highly associated with other neurological disorders. The incidence was much higher in enlisted flyers and enlisted groundcrew than in officers. This finding was independent of group membership. The percentages of Ranch Hands in the maximal cohort with other neurological disorders were 7.4 percent for officers, 32.6 percent for enlisted flyers, and 26.2 percent for enlisted groundcrew. For Comparisons with background levels of current dioxin, the incidences were 7.8 percent for officers, 33.6 percent for enlisted flyers, and 28.1 percent for enlisted groundcrew. Occupation is also highly associated with current levels of dioxin. Enlisted groundcrew have the highest current levels followed by enlisted flyers and officers (see Chapter 2, Dioxin Assay). Consequently, an additional model that included occupation was examined in each analysis. Appendix Table G-3 presents the results of these analyses.

***Model 1: Ranch Hands - $Log_2$ (Initial Dioxin)***

The unadjusted analyses did not find a significant association between initial dioxin and conditions in the other neurological disorders category under the minimal assumption (Table 8-10 [a]: p=0.392), but under the maximal assumption, the relative risk was significantly more than 1 (Table 8-10 [b]: Est. RR=1.24, p<0.001). The percentage of Ranch Hands in the maximal cohort with a post-SEA history of other neurological disorders increased with levels of initial dioxin (11.5%, 23.5%, and 25.8% for the low, medium, and high initial dioxin categories).

## TABLE 8-10.

### Analysis of Other Neurological Disorders

**Ranch Hands - $Log_2$ (Initial Dioxin) - Unadjusted**

| Assumption | Initial Dioxin | n | Percent Yes | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|
| a) Minimal (n=520) | Low | 130 | 16.2 | 1.07 (0.91,1.26) | 0.392 |
| | Medium | 259 | 29.0 | | |
| | High | 131 | 24.4 | | |
| b) Maximal (n=739) | Low | 183 | 11.5 | 1.24 (1.09,1.40) | <0.001 |
| | Medium | 370 | 23.5 | | |
| | High | 186 | 25.8 | | |

**Ranch Hands - $Log_2$ (Initial Dioxin) - Adjusted**

| Assumption | Adj. Relative Risk (95% C.I.)[a] | p-Value | Covariate Remarks |
|---|---|---|---|
| c) Minimal (n=520) | 1.20 (1.01,1.43) | 0.037 | AGE (p<0.001) |
| d) Maximal (n=739) | 1.35 (1.18,1.54) | <0.001 | AGE (p<0.001) |

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

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

## TABLE 8-10. (Continued)

## Analysis of Other Neurological Disorders

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

| Assumption | Time (Yrs.) | Percent Yes/(n) Current Dioxin Low | Medium | High | Est. Relative Risk (95% C.I.)[a] | p-Value |
|---|---|---|---|---|---|---|
| e) Minimal | | | | | | 0.619[b] |
| (n=520) | ≤18.6 | 16.7 (72) | 28.4 (127) | 18.5 (54) | 1.11 (0.85,1.46) | 0.437[c] |
| | >18.6 | 19.0 (58) | 28.8 (132) | 27.3 (77) | 1.02 (0.82,1.26) | 0.858[c] |
| f) Maximal | | | | | | 0.114[b] |
| (n=739) | ≤18.6 | 7.6 (105) | 21.1 (190) | 25.3 (83) | 1.37 (1.12,1.68) | 0.002[c] |
| | >18.6 | 15.4 (78) | 25.7 (179) | 27.9 (104) | 1.11 (0.94,1.31) | 0.204[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 | | | 0.453[b] | AGE (p<0.001) |
| (n=520) | ≤18.6 | 1.35 (1.01,1.79) | 0.041[c] | |
| | >18.6 | 1.18 (0.94,1.47) | 0.156[c] | |
| h) Maximal | | | 0.082[b] | AGE (p<0.001) |
| (n=739) | ≤18.6 | 1.58 (1.27,1.96) | <0.001[c] | |
| | >18.6 | 1.24 (1.05,1.48) | 0.014[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 8-10. (Continued)

## Analysis of Other Neurological Disorders

### 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 | 781 | 21.6 | All Categories | | 0.014 |
| Unknown | 342 | 17.0 | Unknown vs. Background | 0.74 (0.53,1.03) | 0.073 |
| Low | 195 | 27.2 | Low vs. Background | 1.35 (0.94,1.93) | 0.100 |
| High | 187 | 26.7 | High vs. Background | 1.32 (0.92,1.91) | 0.135 |
| Total | 1,505 | | | | |

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

| Current Dioxin Category | n | Contrast | Adj. Relative Risk (95% C.I.) | p-Value | Covariate Remarks |
|---|---|---|---|---|---|
| Background | 781 | All Categories | | <0.001 | AGE (p<0.001) |
| Unknown | 342 | Unknown vs. Background | 0.71 (0.50,0.99) | 0.041 | |
| Low | 195 | Low vs. Background | 1.39 (0.96,2.01) | 0.078 | |
| High | 187 | High vs. Background | 1.72 (1.17,2.51) | 0.005 | |
| Total | 1,505 | | | | |

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.

Adjusting for age, the relative risk was significantly more than 1 under both the minimal (Table 8-10 [c]: Adj. RR=1.20, p=0.037) and maximal (Table 8-10 [d]: Adj. RR=1.35, p<0.001) assumptions. However, the relative risk became nonsignificant under both assumptions, after also including occupation in the model (Appendix Table G-3: Adj. RR=0.97, p=0.740 under the minimal assumption; Adj. RR=1.04, p=0.567 under the maximal assumption).

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

Under the minimal assumption, the unadjusted current dioxin and time since tour analysis of the other neurological disorders category did not find a significant current dioxin-by-time interaction (Table 8-10 [e]: p=0.619). The interaction between current dioxin and time was also not significant under the maximal assumption (Table 8-10 [f]: p=0.114), but there was a significant association between current dioxin and other neurological disorders for Ranch Hands with a later tour (time≤18.6: Est. RR=1.37, p=0.002; % yes: 7.6%, 21.1%, and 25.3% for the low, medium, and high current dioxin categories).

After adjusting for age, the current dioxin-by-time interaction remained nonsignificant under the minimal assumption (Table 8-10 [g]: p=0.453), but the relative risk became significantly more than 1 for Ranch Hands with a later tour (time≤18.6: Adj. RR=1.35, p=0.041). Under the maximal assumption, the association between current dioxin and other neurological disorders differed marginally between time strata (Table 8-10 [h]: p=0.082) after adjusting for age. In each time stratum, the relative risk was significantly more than 1. The relative risk was 1.58 (p<0.001) for Ranch Hands in the maximal cohort with a later tour and 1.24 (p=0.014) for those with an earlier tour. However, adjusting for age and occupation, the current dioxin-by-time interaction and all within time stratum results were not significant under both assumptions (Appendix Table G-3: p>0.10 for all analyses).

***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The incidence of conditions in the other neurological disorders category differed significantly among current dioxin categories in the unadjusted analysis (Table 8-10 [i]: 21.6%, 17.0%, 27.2%, and 26.7% for the background, unknown, low, and high current dioxin categories, p=0.014). The relative risk for the unknown versus background contrast was marginally less than 1 (Est. RR=0.74, 95% C.I.: [0.53,1.03], p=0.073) and marginally more than 1 for the low versus background contrast (Est. RR=1.35, 95% C.I.: [0.94,1.93], p=0.100).

The overall contrast was highly significant after adjusting for age (Table 8-10 [j]: p<0.001). Each Ranch Hand versus background contrast was significant or marginally significant. There was a significant increased risk of other neurological disorders for the high current dioxin category (Adj. RR=1.72, 95% C.I.: [1.17,2.51], p=0.005) and a marginally significant increased risk in the low category (Adj. RR=1.39, 95% C.I.: [0.96,2.01], p=0.078). The relative risk was significantly less than 1 for the unknown category (Adj. RR=0.71, 95% C.I.: [0.50,0.99], p=0.041).

The results of the analyses adjusting for age and occupation were all nonsignificant (Appendix Table G-3: p>0.50 for each contrast). The relative risk for the unknown versus background contrast, which had been significantly less than 1, became more than 1 (Adj.

RR=1.12) and was larger than the relative risk for both the low versus background contrast (Adj. RR=1.09) and the high versus background contrast (Adj. RR=1.06).

### *Physical Examination Variables*

#### Smell

##### *Model 1: Ranch Hands - $Log_2$ (Initial Dioxin)*

Both the minimal and maximal initial dioxin analyses of smell found a relative risk that was less than 1, but not significant (Table 8-11 [a-d]: $p>0.30$ for the unadjusted and adjusted analyses). There were only four Ranch Hands in the minimal cohort and five Ranch Hands in the maximal cohort with an abnormal sense of smell.

##### *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 investigated because only one Ranch Hand with more than 18.6 years since tour had an abnormal sense of smell. The association between current dioxin and smell was not significant for Ranch Hands with 18.6 years or less since tour in the unadjusted analyses (Table 8-11 [e] and [f]: $p=0.375$ for the minimal analysis and $p=0.727$ for the maximal analysis). No adjusted analyses were done because there were so few abnormalities.

##### *Model 3: Ranch Hands and Comparisons by Current Dioxin Category*

The overall contrast was not significant in both the unadjusted and adjusted categorized current dioxin analyses of smell (Table 8-11 [g] and [h]: $p=0.227$ and $p=0.193$, respectively).

#### Visual Fields

##### *Model 1: Ranch Hands - $Log_2$ (Initial Dioxin)*

Under both the minimal and maximal assumptions, there was only one Ranch Hand with a visual field abnormality. Table 8-12 [a] shows that he was in the low initial dioxin category under the minimal assumption. No analyses were performed because of the sparse number of abnormalities.

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

No current dioxin and time since tour analyses were done because there was only one visual field abnormality.

##### *Model 3: Ranch Hands and Comparisons by Current Dioxin Category*

The only two cases with an abnormal visual field were one Comparison in the background category and one Ranch Hand in the unknown current dioxin category. Neither the overall contrast (Table 8-12 [e]: $p=0.313$) nor the unknown versus background contrast

## TABLE 8-11.

### Analysis of Smell

**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=521) | Low | 130 | 0.8 | 0.61 (0.21,1.79) | 0.324 |
| | Medium | 260 | 1.2 | | |
| | High | 131 | 0.0 | | |
| b) Maximal (n=741) | Low | 184 | 0.5 | 0.88 (0.44,1.75) | 0.708 |
| | Medium | 371 | 0.8 | | |
| | High | 186 | 0.5 | | |

**Ranch Hands - $Log_2$ (Initial Dioxin) - Adjusted**

| Assumption | Adj. Relative Risk (95% C.I.)[a] | p-Value | Covariate Remarks |
|---|---|---|---|
| c) Minimal (n=521) | 0.67 (0.22,2.00) | 0.432 | AGE (p=0.421) |
| d) Maximal (n=741) | 0.93 (0.45,1.89) | 0.830 | AGE (p=0.378) |

[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 8-11. (Continued)**

**Analysis of Smell**

**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 | | | | | | -- |
| (n=521) | ≤18.6 | 1.4 (72) | 1.6 (128) | 0.0 (54) | 0.50 (0.11,2.31) | 0.375[b] |
| | >18.6 | 0.0 (58) | 0.8 (132) | 0.0 (77) | -- | -- |
| f) Maximal | | | | | | -- |
| (n=741) | ≤18.6 | 0.9 (106) | 1.6 (191) | 0.0 (83) | 0.86 (0.36,2.03) | 0.727[b] |
| | >18.6 | 0.0 (78) | 0.6 (179) | 0.0 (104) | -- | -- |

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

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

--: Relative risk, confidence interval, 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: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

## TABLE 8-11. (Continued)

## Analysis of Smell

### g) 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 | 784 | 0.8 | All Categories | | 0.227 |
| Unknown | 343 | 0.3 | Unknown vs. Background | 0.38 (0.05,3.16) | 0.640 |
| Low | 196 | 1.5 | Low vs. Background | 2.02 (0.50,8.13) | 0.522 |
| High | 187 | 0.0 | High vs. Background | -- | 0.552 |
| Total | 1,510 | | | | |

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

| Current Dioxin Category | n | Contrast | Adj. Relative Risk (95% C.I.) | p-Value | Covariate Remarks |
|---|---|---|---|---|---|
| Background | 784 | All Categories | | 0.193 | AGE (p=0.176) |
| Unknown | 343 | Unknown vs. Background | 0.37 (0.04,3.09) | 0.359 | |
| Low | 196 | Low vs. Background | 2.05 (0.51,8.28) | 0.317 | |
| High | 187 | High vs. Background | -- | -- | |
| Total | 1,510 | | | | |

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

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

## TABLE 8-12.

## Analysis of Visual Fields

**Ranch Hands - $Log_2$ (Initial Dioxin) - Unadjusted**

| Assumption | Initial Dioxin | n | Percent Abnormal | Est. Relative Risk (95% C.I.) | p-Value |
|---|---|---|---|---|---|
| a) Minimal (n=521) | Low | 130 | 0.8 | -- | -- |
| | Medium | 260 | 0.0 | | |
| | High | 131 | 0.0 | | |
| b) Maximal (n=741) | Low | 184 | 0.0 | -- | -- |
| | Medium | 371 | 0.3 | | |
| | High | 186 | 0.0 | | |

--: 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: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.