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. Marui
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,
CHICAGO, IL

March 1991

Volume II

SERUM DIOXIN ANALYSIS OF 1987 EXAMINATION RESULTS

Contract Number: F41689-86-D-0010
SAIC Project Number: 1-813-X4-196/254/437/011/942/943

AIR FORCE HEALTH STUDY

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

March 1991

VOLUME II

SERUM DIOXIN ANALYSIS OF 1987 EXAMINATION RESULTS

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

TABLE OF CONTENTS

VOLUME II

TABLE OF CONTENTS - REPORT

CHAPTER 7

MALIGNANCY ASSESSMENT

INTRODUCTION

Background

Cancer is a major suspect disease following exposure to chlorophenols, phenoxy herbicides, and dioxin. Both systemic cancer and skin cancer are key focal points of this study. At present, there is no scientific consensus on the dioxin-cancer question. There is, however, concern that some malignancies including soft tissue sarcoma (STS) and non-Hodgkin's lymphoma (NHL) may be associated with dioxin exposure.

Traditional difficulties in extrapolating animal data to humans and interspecies variability have limited the direct applicability of much of the experimental work. Other major challenges have included difficulties in the ability to control or characterize bias; selection of suitable controls or reference groups; quality and quantity of exposure; misclassification of exposure; confounding exposure to known injurious chemicals; sample size and statistical power; number and selection of relevant risk factors; and the lack of clearly defined clinical endpoints for study.

Numerous animal studies have been conducted to delineate the role of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on tumor initiation, tumor promotion, mutagenesis, cocarcinogenesis, and deoxyribonucleic acid (DNA) reactivity. The consensus of most research is that TCDD is only weakly mutagenic, does not covalently bind to DNA or cause it to initiate repair synthesis, but behaves as a strong tumor promoter in already initiated cells (1). Recent animal studies have supported the theory that TCDD-induced response is mediated by a nongenotoxic mechanism. TCDD, binding to the Ah receptor, appears to alter cellular regulatory mechanisms resulting in enhanced cellular proliferation (2-6).

The oncogenic response to TCDD in animals has been shown repeatedly to depend upon the age, sex, and strain of species, as well as the dose and route of administration (7, 8, 9). In the presence of a strong carcinogen, TCDD induced skin papillomas in homozygous hairless mice but not in the heterozygous strain. This clearly supports the promoter role of TCDD, a nongenetic mechanism judged to be related to receptor binding (10).

Studies in rodents produced hepatocellular carcinomas, squamous cell carcinomas of the oropharynx and lung, and follicular cell thyroid adenomas (11, 12, 13). TCDD has been shown to affect the action of estrogen in a number of tissues, possibly leading to carcinogenesis. In rats, TCDD has been shown to promote liver cancer but to inhibit uterine and mammary tumors due to interference with estrogen activity (14, 15). TCDD also exhibits antiestrogenic activity (16, 17, 18) in human cancer cells.

Based upon these and other studies, the International Agency for Research on Cancer designated TCDD as carcinogenic in 1982. There are insufficient data to implicate 2,4-D and 2,4,5-T as carcinogens.

In a series of publications beginning in 1974, commonly known as the "Swedish studies," extensive inquiry was made into occupational cancer following exposure to a variety of herbicides. Four related efforts (19-22) using Swedish railroad workers found an increased cancer incidence associated with non-TCDD containing herbicides. However, a review of these studies by other investigators suggested cancer promotion following phenoxy acid exposure (23).

Prompted by a slight increase in STS in the railroad workers and clinical experience with a case series of STS, Hardell and coworkers launched an extensive second round of studies (24-32). These efforts showed statistically significant increased risks for STS, Hodgkin's Disease (HD), and NHL. For exposure to phenoxy acids alone, the risk ratio ranged from 5.3 to 6.8 for STS in northern and southern Sweden, respectively, while a range of 3.3 to 6.6 was noted for exposure to chlorophenol alone. For malignant lymphoma (HD plus NHL), risk ratios of 8.4 and 4.8 were respectively demonstrated for chlorophenol and phenoxy acid exposures. An association of nasal and nasopharyngeal cancer to chlorophenol exposure (risk ratio, 6.7) was also detected (30), but other specifically focused studies of primary liver cancer and colon cancer were negative with respect to phenoxy acid or chlorophenol exposure (29, 31). The colon cancer study was conducted specifically to demonstrate a lack of respondent bias to "validate" previous questionnaire and interview methods used in the STS studies.

From the outset, the Swedish studies have been criticized on methodologic issues (33, 34, 35), prompting the primary authors, Axelson and Hardell, to respond with clarifications, new calculations, amplifying studies on additional cohorts, and studies on other cancers (29, 32, 36-38). The chief criticisms centered upon possible respondent and observational biases, selection of controls, confounding exposures, and the degree of true exposure to phenoxy acids and chlorophenols. The authors answered these criticisms within the inherent constraints of the case-control methodology. Their efforts have been characterized as careful, clever, and properly stated, and have received favorable reviews (39, 40).

The principal investigators of the Swedish studies have published reports of more recent studies in an attempt to clarify and strengthen their earlier results mentioned above (41, 42). Employing a case-control design and including only cases confirmed by histopathologic examination, they compared 55 cases of STS with 220 living and 110 deceased population-based controls. To reduce the potential impact of exposure recall bias in patients with cancer, a second control group from the same tumor Registry was created which included 190 individuals with forms of cancer other than STS, malignant lymphoma, or nasopharyngeal cancer. Exposure to phenoxyacetic acids was determined by a questionnaire that was followed up by direct telephone contact by trained interviewers blinded to the disease status of participants. The authors concluded that the relative risk for STS in the exposed group was 3.3 (95% C.I.: [1.4,8.1]) when compared to the population-based control group and 2.2 (95% C.I.: [0.9,5.3]) relative to the controls with other forms of cancer.

Though the results of this study tend to confirm the authors' previous observations, the relative risk for developing STS was considerably lower than that found in the earlier studies. Furthermore, when compared with the control group with other forms of cancer, the relative risk was not statistically significant. In contrast to previous studies, the authors found no increased risk for STS in association with chlorophenol exposure. Finally, the authors

acknowledge that a principal limitation in all the occupational studies to date has been the difficulty in determining whether risk is associated with exposure to phenoxyacetic acids or to contaminants such as 2,3,7,8-TCDD. In their most recent study, the authors cited evidence that the increased risk of STS may in fact be due to other higher chlorinated isomers of dioxin (42).

Four small industrial mortality studies were conducted in the late 1970's and early 1980's (43-46). National Institute for Occupational Safety and Health investigators pooled the data from these studies and noted that 3 of the 105 deaths (2.9%) in these studies were due to STS, as contrasted to an expected 0.07 percent in the U.S. general population (47). This study was criticized for the addition of possibly noncomparable industrial cohorts and the lack of histologic confirmation of the STS cases. A subsequent case report added another STS case to the industrial studies (48), and two other reports revealed three unrelated STS cases also arising from the industrial sector (49, 50). However, upon closer inspection, only two of the first four cases were confirmed as STS by an independent histologic review (51). Other reviews of the seven total cases were noteworthy: there was poor agreement on the histologic subtype of the soft tissue tumors, and, because of a feature of the International Classification of Diseases, 9th Revision, (ICD-9) system, wherein organ-specific sarcomas are coded separately from soft and connective tissue tumors (ICD code 171), death certificate-based studies underascertain STS by approximately 40 percent (51, 52). (This latter problem did not affect the Swedish studies.) Two studies of workers from Dow Chemical's Midland facility have indicated slightly increased levels of some cancers (primarily soft tissue), but none of statistical significance (53, 54). A study of workers exposed during a 1953 accident at a BASF plant in Germany also showed no statistically significant increases in cancers, but this study may have suffered from an insufficient cohort size (55).

Other cancer studies throughout the world showed mixed support for the Swedish findings. An Italian case-control effort (56) showed a weak association between ovarian mesothelial tumors and herbicide exposure, whereas a Finnish study of a small number of pesticide sprayers understandably did not detect any cases of STS or malignant lymphomas (ML) (57). A study of more than 4,000 Danish phenoxy herbicide workers noted five STS cases (versus 1.8 expected) and seven ML cases (versus 5.4 expected) (58). The author concluded that the STS observation supported the Swedish work and that the ML data did not.

One New Zealand case-control study showed a nonsignificant relative risk of 1.3 for STS among occupations consistent with phenoxy herbicide exposure (59), although a risk of 7.2 was noted for STS and potential chlorophenol exposure in tanneries.

A related cancer registry-based, case-control study revealed significant excesses of agricultural and forestry occupations from ML cases and multiple myeloma cases (odds ratio 1.25) (60). A recent (1987) expanded version of this study found no increase in risk of NHL and no trend toward increasing risk with increasing duration and intensity of exposure (61). In a similar but larger cancer registry study in Sweden, there was no increased risk of STS (relative risk: 0.9) in agricultural or forestry workers as contrasted to other industrial workers (62). Furthermore, the STS risk was constant over time in spite of an increased

usage of phenoxy acid herbicides from 1947 to 1970. This Swedish study did not confirm or show a trend consistent with the earlier Hardell studies.

Other recent occupational epidemiologic studies have focused on the incidence of lymphoma in agricultural workers. Using a similar protocol, other Swedish investigators expanded a previous study cited above (62) to include an analysis of HD and NHL (63). In the total study cohort, which was made up of 354,620 men employed in various forestry and agriculture occupations, no increase in the relative risk for NHL was found. Statistically significant elevations in relative risk for HD were found in two subcohorts, but further analysis failed to support an association with herbicide exposure. Of the 15 cases of HD in silviculture workers, 8 occurred in managers or administrators.

The principal limitation of uncertain exposure in this and other studies (64, 65) was addressed in a recent mortality study of 322 Dow Chemical employees who met probable or definite criteria for chloracne, an undisputed marker of high level exposure to dioxins and related compounds (66). Thirty-three deaths occurred in the study cohort versus 39.5 expected. None of the deaths was related to the suspect cancers listed above.

A recent U.S. case-control study from the Kansas cancer registry has provided partial support for Hardell's observations (67). The Kansas study was very similar in methodology to the early Swedish studies and tried to avoid bias and misclassification. An overall relative risk of 1.6 was found for NHL in men exposed to herbicides, particularly 2,4-D. As the frequency of herbicide exposure increased to more than 20 days per year, the relative risk of NHL increased to 6.0 as compared to nonfarmers. For herbicide applicators, the relative risk for NHL was 8.0. A simultaneously published review of the Kansas work noted that this should shift scientific concern from STS to NHL (68). A population-based, case-control study of STS and NHL in western Washington found no overall increased risk of these diseases associated with an occupational history of exposure to chlorophenols or phenoxy herbicides (69). However, risks of NHL were significantly elevated in the specific occupational categories of farmers, forestry herbicide applicators, and individuals potentially exposed to phenoxy herbicides in any occupation for 15 years or more. An increased risk of NHL was also noted among those with occupational exposure to insecticides, organic solvents, lead, and welding fumes.

Several studies of Vietnam veterans have attempted to determine whether veterans have experienced excessive mortality, particularly from cancer (70-77). Most of the studies used proportionate mortality ratio (PMR) methodology and equated Vietnam service with potential exposure to Agent Orange, a procedure of considerable imprecision (misclassification). These exposure allocation difficulties, coupled with the inherent methodological weaknesses of the PMR technique, have minimized the contribution of these studies to the clarification of the cancer issue.

Several important studies of the incidence of cancer in Vietnam veterans have recently been published, although, with the exception of the Air Force Health Study (AFHS), they have not been designed to relate the incidence of cancer to herbicide exposure. The mortality component of the Vietnam Experience Study by the U.S. Centers for Disease Control (CDC) found the overall mortality from cancer to be similar in Vietnam and non-Vietnam veterans

(78). In a cohort mortality study of Army and Marine Corps veterans (79), service in Vietnam was associated with a slightly elevated proportionate mortality ratio for all causes of cancer and, for cancers at specific sites, an increase in mortality rates due to lung cancer and NHL. Neither Army nor Marine veterans had an apparent increase in risk for STS.

In the latest report of the third examination cycle of the AFHS, the frequency of systemic cancer for Ranch Hands and Comparisons was similar (80). Ranch Hand participants continued to have a greater incidence of basal cell skin cancer. Mortality studies have shown no significant differences between the Ranch Hand and Comparison cohorts (81).

To date, almost all of the studies of veterans were negative for aggregate cancer associations. As an example of the veteran studies, the Australian retrospective cohort mortality effort revealed an overall relative mortality ratio of 0.99, an overall cancer mortality ratio of 0.95, and nonsignificant statistical differences for STS, NHL, and HD (73). Two more recent case-control studies found no evidence for an increased risk of STS in association with military service in Vietnam (82, 83).

The recently released (though not yet published) Selected Cancers Study (SCS) of the U.S. CDC focused more specifically on the incidence in Vietnam veterans of the NHL, STS, HD, nasal and nasopharyngeal carcinoma, and primary liver cancer. The case-control design of the study was selected as one that requires fewer subjects than a cohort study and as the only feasible method for studying rare cancers with a long latency period. The SCS was designed to compare the risk of specific cancers among Vietnam veterans relative to that in men with no military service in Vietnam. This study was based on diagnoses of malignant disease reported by eight tumor registries in the United States, providing surveillance of 10 percent of the total U.S. population. The comparison group was drawn from random telephone interviews and included men of the same age who did not have any of the six cancers under study. Interviews were based on a standardized questionnaire with high participation in both case (87%) and control (85%) groups. The relative risk of the specific cancers occurring in association with military service in Vietnam was determined by an odds ratio (OR).

Results of the SCS defined a statistically significant ($p=0.01$) increase in relative risk (RR=1.47; 95% C.I.: [1.09,1.97]) for the development of NHL in Vietnam versus non-Vietnam veterans. Further analysis failed to reveal any significant increase in risk related to age at time of service, rank, or job description (combat, combat support, or support). Navy and Marine veterans were at a slightly greater risk but the difference was not statistically significant. Pertinent to the current report, there was no evidence that the increased risk of NHL was associated with factors thought to indicate an increased likelihood of herbicide exposure. Furthermore, Vietnam veterans who served in III Corps (the combat zone with the heaviest use of Agent Orange) were at slightly lower risk than veterans serving in other regions.

More detailed summaries of the pertinent scientific literature for the malignancy assessment can be found in the report of the previous analyses of the 1987 examination data (80).

Summary of Previous Analyses of the 1987 Examination Data

The unadjusted analysis of all verified neoplasms indicated that the proportion of Ranch Hands with neoplasms was significantly greater than that of the Comparisons. After including suspected neoplasms with verified neoplasms, the Ranch Hand proportion was marginally greater than the Comparison proportion. The majority of malignant neoplasms observed in the Ranch Hands were basal cell carcinomas, a nonlife-threatening form of skin cancer. When the analysis was performed only on skin neoplasms for non-Black participants, significantly more Ranch Hands had skin neoplasms than did the Comparisons for both the verified and the verified and suspected diagnoses. A significantly greater proportion of Ranch Hands had verified malignant skin neoplasms than did the Comparisons. Given the presence of a neoplasm, a marginally significant higher proportion of Ranch Hands had skin neoplasms than did the Comparisons.

In the unadjusted analyses of verified basal cell carcinoma, a marginally significant group difference was found. The unadjusted analysis of the verified and suspected basal cell carcinomas was not significant. After adjustment for covariates, the group contrast was statistically significant for verified basal cell carcinoma and marginally significant for the verified and suspected diagnoses. Ranch Hands and Comparisons differed significantly on the frequency of participants with zero, one, or multiple verified basal cell carcinomas. Also, the Ranch Hands had a significantly higher percentage of participants with multiple verified basal cell carcinomas than did the Comparisons.

Sun exposure-related malignant skin neoplasms also exhibited group differences. (Approximately 90 percent of the participants with sun exposure-related malignant neoplasms had basal cell carcinomas.) For the unadjusted analysis, the group contrast was significant for the verified diagnoses and marginally significant for the combination of verified and suspected sun exposure-related malignant skin neoplasms. For the adjusted analysis of these neoplasms, the Ranch Hands and Comparisons differed significantly for both the verified and combined diagnoses.

No significant group differences were found in the analyses of systemic neoplasms by number, behavior (malignant, benign, uncertain behavior, or unspecified nature), or by location and site. Thus, the increase in overall malignancy was due to elevated relative risks for skin cancer (basal cell carcinoma). Also, given the presence of any systemic neoplasm, Ranch Hands and Comparisons did not differ significantly for malignant systemic neoplasms. The number of STS and NHL was comparable in the two groups. For the 1985 examination, one Ranch Hand and one Comparison had verified STS (fibrous histiocytoma and fibrosarcoma, respectively). The Ranch Hand was not part of the 1987 study because he died; the Comparison with the fibrosarcoma was part of the 1987 examination. At the 1985 examination, one Ranch Hand was classified as having a suspected leukemia, HD, or NHL. He was diagnosed as a verified leukemia by the time of the 1987 examination. At the 1987 examination, there was one verified case of NHL in a Ranch Hand.

The fixed size of the Ranch Hand cohort limited the ability of the study to detect group differences for the rare forms of cancer (particularly STS and NHL). The study had virtually no statistical power to detect low to moderate group differences for these malignancies. The study had good power to detect relative risks of 2.0 or more with respect to disease occurring

at prevalences of at least 5 percent in the Comparison group, such as basal cell carcinoma and all systemic cancers combined.

Parameters for the Malignancy Assessment

Dependent Variables

The malignancy assessment was based on lifetime incidence of neoplasms exclusive of the neoplasms occurring before the Southeast Asia (SEA) tours of duty. Information on the occurrence of neoplasms was captured in the health questionnaires and the physical examinations at Baseline (1982) and the 1985 and 1987 studies and was coded according to conventions in the International Classification of Diseases, 9th Edition, Clinical Modification manual. Information on neoplasms from the questionnaire and the physical examination were combined to form a lifetime incidence of neoplasms for each participant.

The term "neoplasm" refers to any new growth that may or may not be malignant. Malignant neoplasms are those neoplasms capable of invasion and metastasis. Malignant and benign neoplasms, carcinomas in situ, and neoplasms of uncertain behavior or unspecified nature as well as skin and systemic neoplasms were studied. Systemic neoplasm was used to denote a nonskin neoplasm.

The malignancy assessment was based on the number of participants in the 1987 study with serum dioxin assays, and not on the number of neoplasms. A participant was considered to have an adverse health condition for the malignancy assessment if he had one or more neoplasms.

Questionnaire and Physical Examination Data

During the 1987 health interview, each study participant was asked a series of questions on the incidence of cancer since the date of his last health interview. Participants who were new to the AFHS also completed the Baseline health questionnaire. The self-reported conditions were verified by medical record review. The verification status of each self-reported neoplasm was classified as (1) verified (supported by medical record), (2) nonverifiable (not supported by medical record), or (3) pending (medical record not yet provided). The reported neoplasms for which the verification status is pending were called suspected neoplasms. Only data on verified or suspected neoplasms were used in the malignancy assessment. All reported neoplasms in the Ranch Hands were verified. Suspected neoplasms only occurred among the Comparisons.

Some possible neoplastic conditions were discovered by the physicians at the physical examination. Contingent upon participant authorization, suspicious skin lesions were biopsied, and the pathology was determined; however, no invasive procedures were used to detect systemic neoplasms. For some suspicious skin lesions and suspected systemic neoplasms, the verification process had not been completed by the time of the data analysis. Both the verified and suspected (verification not completed) neoplasms from the physical examination were used in the analysis. This was deemed necessary in order to describe the complete neoplasm findings, recognizing that confirmation of all suspected cases was difficult.

Skin Neoplasms

The analysis of skin neoplasms for the malignancy assessment was divided into four sets. Each set was analyzed for an association with initial dioxin, with current dioxin and time since tour, and with categorized current dioxin. The first two types of analyses (i.e., Ranch Hand-only analyses) used verified skin neoplasms only because there were no unconfirmed cases. For the analysis using categorized current dioxin, verified skin neoplasms were analyzed as well as the combination of verified and suspected neoplasms, wherever possible.

Analysis set 1 consisted of analyses of skin neoplasms by behavior. Four behavior types were examined: (1) all skin neoplasms, (2) malignant neoplasms only, (3) benign neoplasms only, and (4) neoplasms of uncertain behavior or unspecified nature.

Analysis set 2 consisted of analyses of malignant skin neoplasms by cell type. Four types were analyzed: (1) basal cell carcinoma, (2) sun exposure-related malignant skin neoplasms (basal cell carcinoma, squamous cell carcinoma, melanoma, and malignant epithelial neoplasms not otherwise specified [NOS]), (3) melanoma, and (4) squamous cell carcinoma. Analyses of basal cell carcinoma, melanoma, and sun exposure-related malignant skin neoplasms were conducted for all sites combined and by location/site. Five locations/sites were examined: (1) ear, face, head, and neck; (2) trunk; (3) upper extremities; (4) lower extremities; and (5) other sites (including sites NOS). Squamous cell carcinoma was analyzed for all sites combined.

Analysis set 3 consisted of analyses of basal cell carcinoma and sun exposure-related malignant skin neoplasms by occupation. For both groups of neoplasms, the analyses were performed on the number of participants with neoplasms on the ear, face, head, and neck, as compared to the number of participants with no neoplasms. These analyses were repeated using all other sites combined.

In addition, an analysis of participants having one or more basal cell carcinomas versus no basal cell carcinomas was conducted.

Because there were relatively few Blacks in this study (n=32 for the minimal assumption; n=38 for the maximal assumption; and n=80 for the categorized current dioxin analyses), and since Black participants exhibited only benign skin neoplasms, most of the subsequent analyses were limited to non-Blacks. However, both Blacks and non-Blacks were combined in the analysis of benign skin neoplasms. No participants were excluded for medical reasons from the analysis of these variables.

Systemic Neoplasms

The systemic neoplasms were analyzed by behavior and body site. As with skin neoplasms, each analysis was conducted using verified data and, when possible, also verified and suspected neoplasms. The analysis of the systemic neoplasms was divided into two sets, described below.

Analysis set 1 consisted of analyses of systemic neoplasms by behavior. Four behavior types were examined: (1) all systemic neoplasms, (2) malignant neoplasms, (3) benign neoplasms, and (4) neoplasms of uncertain behavior or unspecified nature.

Analysis set 2 consisted of analyses of malignant systemic neoplasms by site: (1) ear, head, face, and neck; (2) oral cavity, pharynx, and larynx; (3) brain; (4) thymus and mediastinum; (5) thyroid; (6) bronchus and lung; (7) colon and rectum; (8) kidney and bladder; (9) prostate; (10) testicles; (11) ill-defined sites; (12) carcinoma in situ of penis; and (13) carcinoma in situ of other and unspecified sites.

In addition to the analyses described above, the number of participants with Hodgkin's disease, leukemia, and malignant neoplasms of lymphoid and histiocytic tissue were analyzed.

No participants were excluded for medical reasons from the analysis of these variables.

Skin and Systemic Neoplasms

All neoplasms, skin and systemic combined, were analyzed for an association with initial dioxin, with current dioxin and time since tour, and with categorized current dioxin. As in analyses of skin neoplasms only and systemic neoplasms only, the Ranch Hand-only analyses were performed using verified diagnoses. The categorized current dioxin analysis was performed using participants with a verified neoplasm and using participants with verified and suspected neoplasms.

There were no medical exclusions in the analysis of these variables.

Covariates

The emphasis on cancer was increased during the 1985 study. In particular, the interval health questionnaire was modified to collect information on each geographic location in which a participant lived for more than 12 months. Because ultraviolet light exposure has been acknowledged as the primary cause of basal cell carcinoma, this information was used to compute a cumulative sun-exposure index based on residential history. An average lifetime residential latitude was estimated by dividing the total degree-years (i.e., the sum of the product of latitude [degrees] and the number of years lived at each residence) from all residences by the total number of residential years reported on the questionnaire. In addition, detailed information on skin tannability; eye, skin, and hair color; parental ethnicity; and lifetime smoking history was obtained. This information was obtained for participants in the 1987 examination who did not attend the 1985 examination.

In the 1987 examination, the questionnaire was expanded to capture a detailed history of alcohol consumption. Baseline questions on exposure to carcinogens were repeated to collect interval data. Interval smoking patterns were also captured.

In the analysis of the 1987 examination results, 33 covariates were candidates for adjusted statistical analyses assessing basal cell carcinoma and sun exposure-related malignant skin neoplasms. Analyses of skin neoplasms were limited to non-Blacks.

Candidate covariates included age, lifetime cigarette smoking history, lifetime alcohol history, ethnic background, skin color, hair color, eye color, reaction of skin to sun exposure, the composite sun-reaction index, average lifetime residential latitude, and exposure to individual carcinogens and groups of carcinogens. For lifetime cigarette smoking history and lifetime alcohol history, the respondent's average daily smoking and average daily alcohol consumptions were estimated over his lifetime, assuming 365 packs of cigarettes equaled 1 pack-year and 365 drinks equaled 1 drink-year, respectively.

The candidate covariates for the systemic malignancy assessment were the same as those for the skin malignancy assessment with the following exceptions:

- Race was added as a candidate covariate.
- The following covariates specific to skin were deleted: ethnic background, skin color, hair color, eye color, reaction of skin to sun exposure, sun-reaction index, and average lifetime residential latitude.

Definitions and categories of candidate covariates are provided below:

- Ethnic Background: (A) English, Welsh, Scottish, or Irish; (B) Scandinavian, German, Polish, Russian, other Slavic, Jewish, or French; (C) Spanish, Italian, or Greek; (D) Mexican, American Indian, or Asian; and (E) African.
- Skin Color: dark, medium, pale, dark peach, and pale peach.
- Hair Color: black, dark brown, light brown, blonde, and red.
- Eye Color: brown, hazel, green, gray, and blue.
- Two reactions of the skin to sun exposure:
  1) At Least 2 Hours Sun Exposure, After First Exposure: burns painfully, burns, becomes red, and no reaction.
  2) After Repeated Sun Exposures: freckles with no tan, tans mildly, tans moderately, and tans deep brown.
- Composite Sun-Reaction Index: a composite variable based on two reaction of skin to sun exposure variables was defined as follows: (1) burns painfully and/or freckles with no tan, (2) burns and/or tans mildly, and (3) all other reactions.
- Average Lifetime Residential Latitude: average latitude less than 37 degrees and average greater than or equal to 37 degrees.
- Exposure to Carcinogens or Groups of Carcinogens:
  Set 1: asbestos, ionizing radiation, industrial chemicals, herbicides, insecticides, and degreasing chemicals (yes/no for each).
  Set 2: anthracene, arsenic, benzene, benzidine, chromates, coal tar, creosote, aminodiphenyl, chloromethyl ether, mustard gas, naphthylamine, cutting oils, trichloroethylene, ultraviolet light (not sun), and vinyl chloride (yes/no for each).

Composite Carcinogen Exposure Index: yes, if exposure to any carcinogen in set 2; no, otherwise. Self-reported information on exposure to the 15 individual carcinogens of set 2 was obtained at the physical examination. Because substantially fewer participants reported exposure to the individual carcinogens than those of the questionnaire-based items addressing the individual carcinogens in set 1, and in the interest of reducing the number of possible covariates, a composite carcinogen exposure index was constructed from the set of 15 carcinogens.

As described in the previous report on the 1987 examination study (see page 10-10, [80]), the malignancy assessment contained more than 30 candidate covariates for use in adjusted analyses of skin and/or systemic neoplasms. Because of the large number of covariates, a reduced set of candidate covariates was determined for the analyses of the skin neoplasms by examination of the dependent variable-covariate associations and a statistical screening procedure (see pages 10-44, 10-45, and Appendix Table G-2, [80]). Based on these evaluations, the covariates of age, skin reaction after at least 2 hours of sun exposure, skin reaction after repeated sun exposure, ethnic background, average lifetime residential latitude, and ionizing radiation exposure were selected as covariates to be evaluated under the stepwise modeling procedure. (Occupation was also a covariate included in the skin neoplasm analyses of the 1987 examination report [80]; however, because of its implicit strong association with dioxin, it is not used as a candidate covariate for the serum dioxin analyses.) An examination of the associations between dioxin and the individual covariates resulted in expanding the above group of six covariates to also include hair color in the stepwise modeling procedure for the serum dioxin analyses of the skin neoplasms.

Also, as documented in the 1987 examination report (see page 10-57, [80]), age, race, lifetime cigarette smoking history, and lifetime alcohol history were covariates used in the stepwise modeling procedure for the adjusted analyses of the systemic neoplasms. (Occupation was also used in the adjusted analyses; however, as noted earlier, it is not being used for the serum dioxin analysis.) Based on an examination of the associations between dioxin and individual covariates, as well as the associations between individual covariates and groups of systemic neoplasms (i.e., all systemic, malignant systemic, benign systemic neoplasms), the composite carcinogen exposure index was included with the other covariates of age, race, lifetime cigarette smoking, and lifetime alcohol history for use in the stepwise modeling procedure for the serum dioxin analyses of the systemic neoplasms.

Relation to Baseline, 1985, and 1987 Studies

Most dependent variables and covariates analyzed in the serum dioxin analyses of the malignancy data were analyzed in the 1985 and 1987 studies. Basal cell carcinoma replaced a similar analysis involving nonmelanoma malignant skin neoplasms by location and occupation. In general, the same variables were analyzed in the Baseline study, although less covariate information was captured at that time.

Statistical Methods

Chapter 4, Statistical Methods, describes the basic statistical analysis methods to be used in the malignancy assessment.

Table 7-1 summarizes the statistical analyses that were performed for the malignancy assessment. The first part of this table identifies the dependent variables and the statistical methods. This information is presented in three sections: skin neoplasms, systemic neoplasms, and skin and systemic neoplasms. Data source, data form, cutpoints, and candidate covariates are summarized at the end of the table. The second part of the table describes the candidate covariates. Abbreviations are used in the body of the table and are defined in footnotes. Table 7-2 summarizes the number of participants with missing data on specified covariates.

Appendix F contains graphic displays of relative frequencies of Ranch Hands with a specified neoplasm versus initial dioxin under the minimal and maximal assumptions and relative frequencies of Ranch Hands and Comparisons with a specified neoplasm versus current dioxin. Appendix F also presents graphics for dioxin-by-covariate interactions determined by various statistical models.

Appendix Table F-1 presents tabular displays of these dioxin-by-covariate interactions. In addition, Appendix Tables F-2 through F-5 contain listings, by group, of skin and systemic neoplasm conditions used in the analyses.

Three statistical approaches were used to examine the association between the frequency of participants with a specified neoplasm 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 (80). All three models were implemented with and without covariate adjustment. Chapter 4 provides a more detailed discussion of the models.

RESULTS

Exposure Analysis

Questionnaire and Physical Examination Data

In the malignancy assessment of the report on the 1987 examination results, statistical analyses were performed separately for participants with a verified neoplasm only and for participants with verified and suspected neoplasms combined. For the serum dioxin report, most of the neoplasms were verified (only two participants, both Comparisons, had a suspected neoplasm that was not verified). In particular, for analyses involving only Ranch Hands (i.e., initial dioxin analyses, current dioxin and time since tour analyses), only verified neoplasms were analyzed because no Ranch Hands had a suspected neoplasm. For analyses involving both Ranch Hands and Comparisons (i.e., the categorized current dioxin

TABLE 7-1.

Statistical Analysis for the Malignancy Assessment

Dependent Variables

Category	Location/ Site	Statistical Analyses
Skin Neoplasms		
Behavior		
All	All	U:LR A:LR
Malignant	All	U:LR A:LR
Benign	All	U:LR A:LR
Uncertain Behavior or Unspecified Nature	All	U:LR,CS,FT A:LR
Cell Type and Location/Site		
Basal Cell Carcinoma	All Sites Combined Ear, Face, Head, and Neck Trunk Upper Extremities Lower Extremities Other Sites and NOS	U:LR,CS,FT A:LR
Sun Exposure-Related Malignant	All Sites Combined Ear, Face, Head, and Neck Trunk Upper Extremities Lower Extremities Other Sites and NOS	U:LR,CS,FT A:LR

TABLE 7-1. (Continued)

Statistical Analysis for the Malignancy Assessment

Dependent Variables

Category	Location/ Site	Statistical Analyses
	Skin Neoplasms	
Melanoma	All Sites Combined	U:LR,CS,FT
	Ear, Face, Head, and Neck	A:LR
	Trunk	
	Upper Extremities	
	Lower Extremities	
	Other Sites and NOS	
Squamous Cell Carcinoma	All Sites Combined	U:LR,CS,FT
		A:LR
Cell Type and Location/Site by Occupation		
Basal Cell Carcinoma	Ear, Face, Head, and Neck	U:LR,CS,FT
	All Other Sites and NOS	A:LR
	None	
Sun Exposure-Related Malignant	Ear, Face, Head, and Neck	U:LR,CS,FT
	All Other Sites and NOS	A:LR
	None	
	Skin Neoplasms	
Multiple Basal Cell Carcinoma	All	U:LR,CS,FT
		A:LR
	Systemic Neoplasms	
All	All	U:LR
		A:LR
Malignant	All	U:LR,CS,FT
		A:LR
Benign	All	U:LR
		A:LR
Uncertain Behavior or Unspecified Nature	All	U:LR,CS,FT
		A:LR

TABLE 7-1. (Continued)

Statistical Analysis for the Malignancy Assessment

Dependent Variables

Category	Location/ Site	Statistical Analyses
Location/Site		
Malignant	Ear, Face, Head, and Neck	U:LR,CS,FT A:LR
Malignant	Oral Cavity, Pharynx, and Larynx	U:LR,CS,FT A:LR
Malignant	Brain	U:LR,CS,FT A:LR
Malignant	Thymus and Mediastinum	U:LR,CS,FT A:LR
Malignant	Thyroid Gland	U:LR,CS,FT A:LR
	Systemic Neoplasms	
Malignant	Bronchus and Lung	U:LR,CS,FT A:LR
Malignant	Colon and Rectum	U:LR,CS,FT A:LR
Malignant	Kidney and Bladder	U:LR,CS,FT A:LR
Malignant	Prostate	U:LR,CS,FT A:LR
Malignant	Testicles	U:LR,CS,FT A:LR
Malignant	Ill-Defined Sites	U:LR A:LR
Carcinoma In Situ	Penis	U:LR,CS,FT A:LR

TABLE 7-1. (Continued)

Statistical Analysis for the Malignancy Assessment

Dependent Variables

Category	Location/ Site	Statistical Analyses
Carcinoma In Situ	Other and Unspecified Sites	U:LR A:LR
Hodgkin's Disease	--	U:LR,CS,FT A:LR
Leukemia	--	U:LR,CS,FT A:LR
Other Malignant Neoplasms of Lymphoid and Histiocytic Tissue	--	U:LR,CS,FT A:LR
Skin and Systemic Neoplasms		
All	All	U:LR A:LR

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	C	--
Race (RACE)	MIL	D	Black Non-Black
Lifetime Cigarette Smoking History (PACKYR) (pack-years)	Q-SR	C	--
Lifetime Alcohol History (DRKYR) (drink-years)	Q-SR	C	--

TABLE 7-1. (Continued)

Statistical Analysis for the Malignancy Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Ethnic Background (ETHBACK)	Q-SR (1985)	D	A: English, Welsh, Scottish, or Irish B: Scandinavian, German, Polish, Russian, other Slavic, Jewish, or French C: Spanish, Italian, or Greek D: Mexican, American Indian, or Asian E: African
Skin Color (SKIN)	PE (1985)	D	Dark Medium Pale Dark Peach Pale Peach
Hair Color (HAIR)	PE (1985)	D	Black Dark Brown Light Brown Blonde Red
Eye Color (EYE)	PE (1985)	D	Brown Hazel Green Gray Blue
Reaction of Skin to Sun After at Least 2 Hours, After First Exposure (SUN2HR)	Q-SR	D	Burns Painfully Burns Becomes Red No Reaction
Reaction of Skin to Sun After Repeated Exposure (SUNRPT)	Q-SR	D	Freckles With No Tan Tans Mildly Tans Moderately Tans Deep Brown

TABLE 7-1. (Continued)

Statistical Analysis for the Malignancy Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Composite Sun-Reaction Index (SUNREAC)	Q-SR	D	Burns Painfully (for SUN2HR) or Freckles With No Tan (for SUNRPT) Burns (for SUN2HR) or Tans Mildly (for SUNRPT) All Other Reactions
Average Lifetime Residential Latitude (LAT)	Q-SR (1985)	D	Latitude <37° Latitude ≥37°
Asbestos Exposure (ASB)	Q-SR	D	Yes No
Ionizing Radiation (XRAY)	Q-SR	D	Yes No
Industrial Chemical Exposure (IC)	Q-SR	D	Yes No
Herbicide Exposure (HERB)	Q-SR	D	Yes No
Insecticide Exposure (INS)	Q-SR	D	Yes No
Degreasing Chemical Exposure (DC)	Q-SR	D	Yes No
Anthracene Exposure (ANTH)	Q-SR	D	Yes No
Arsenic Exposure (ARS)	Q-SR	D	Yes No
Benzene Exposure (BENZ)	Q-SR	D	Yes No
Benzidine Exposure (BENZID)	Q-SR	D	Yes No

TABLE 7-1. (Continued)

Statistical Analysis for the Malignancy Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Chromate Exposure (CHROM)	Q-SR	D	Yes No
Coal Tar Exposure (COALTAR)	Q-SR	D	Yes No
Creosote Exposure (CREOS)	Q-SR	D	Yes No
Aminodiphenyl Exposure (AMDIPHEN)	Q-SR	D	Yes No
Chloromethyl Ether Exposure (CHLMETETH)	Q-SR	D	Yes No
Mustard Gas Exposure (MUSTGAS)	Q-SR	D	Yes No
Naphthylamine Exposure (NAPTHYL)	Q-SR	D	Yes No
Cutting Oil Exposure (CUTOIL)	Q-SR	D	Yes No
Trichloroethylene Exposure (TRICHLETH)	Q-SR	D	Yes No
Ultraviolet Light (Not Sun) Exposure (ULTLIGHT)	Q-SR	D	Yes No
Vinyl Chloride Exposure (VINCHL)	Q-SR	D	Yes No
Composite Carcinogen Exposure (CARCIN)	Q-SR	D	Yes No

TABLE 7-1. (Continued)

Statistical Analysis for the Malignancy Assessment

Dependent Variables

Data Source: All AFHS questionnaires and physical examinations

Data Form: Discrete

Cutpoints: Yes/No

Candidate Covariates for Skin Neoplasms: All covariates listed above except race.

Candidate Covariates for Systemic Neoplasms: All covariates listed above except ethnic background, skin color, hair color, eye color, reaction of skin to sun exposure variables, composite sun-reaction index, and average lifetime residential latitude.

Abbreviations

Data Source:
- MIL--Air Force military records
- Q-SR--1987 questionnaire (self-reported)
- Q-SR (1985)--1985 questionnaire (self-reported); updated for participants who attended the 1987 study but not the 1985 study
- PE--1987 physical examination
- PE (1985)--1985 physical examination; updated for participants who attended the 1987 study but not the 1985 study.

Data Form:
- D--Discrete analysis only

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

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

Other:
- NOS--Not otherwise specified

TABLE 7-2.

Number of Participants With Missing Data for the Malignancy Assessment

Variable	Variable Use	Assumption (Ranch Hands Only) Minimal	Assumption (Ranch Hands Only) Maximal	Categorized Current Dioxin Ranch Hand	Categorized Current Dioxin Comparison
Ethnic Background[a]	COV	13	17	16	15
Hair Color[a]	COV	0	0	0	1
Reaction of Skin to Sun After Repeated Exposure[a]	COV	0	0	0	1
Average Lifetime Residential Latitude[a]	COV	0	0	1	5
Lifetime Alcohol History	COV	6	9	9	2
Composite Carcinogen Exposure	COV	6	11	10	7

[a]Non-Blacks only.
COV--Covariate (missing data).

analysis), separate analyses were performed for verified neoplasms and for the combination of verified and suspected neoplasms when suspected neoplasms were present. When a portion of an individual table presents results on the categorized current dioxin analysis, a subtitle identifies whether participants with verified or verified and suspected neoplasms were used. When no suspected neoplasms are present for a dependent variable, only tables labeled as "verified" are provided.

In some analyses, the number of participants with a neoplasm was very sparse or zero, thereby precluding an unadjusted and/or adjusted analysis. For completeness of documentation on such analyses, the relative frequencies and sample sizes are provided without the associated relative risks, confidence intervals, and p-values.

All Skin Neoplasms

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal and maximal assumptions, the unadjusted analyses of the frequency of Ranch Hands with a verified skin neoplasm (regardless of behavior or cell type) exhibited significant or marginally significant relative risks less than 1 with respect to initial dioxin (Table 7-3 [a] and [b]: Est. RR=0.77, p=0.014 and Est. RR=0.88, p=0.092, respectively). For the minimal analysis, the relative frequencies of Ranch Hands with a verified skin neoplasm were 22.9, 15.2, and 12.5 percent within the low, medium, and high initial dioxin categories. The corresponding relative frequencies of Ranch Hands under the maximal assumption were 16.6, 17.7, and 12.3 percent.

Under the minimal assumption, the adjusted analysis of the frequency of Ranch Hands with a verified skin neoplasm also exhibited a significant relative risk (Table 7-3 [c]: Adj. RR=0.77, p=0.021), but it was less than 1. Under the maximal assumption, the relative risk became nonsignificant after adjusting for age, skin reaction after at least 2 hours of sun exposure, and ethnic background (Table 7-3 [d]: p=0.278).

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

Under the minimal assumption, the unadjusted analysis of the frequency of Ranch Hands with a verified skin neoplasm had a nonsignificant interaction between current dioxin and time since tour (Table 7-3 [e]: p=0.646). Although the interaction was nonsignificant, the relative risk within each time stratum was marginally significant but less than 1 (≤18.6 years: Est. RR=0.69, p=0.054; >18.6 years: Est. RR=0.77, p=0.083). The relative frequencies of Ranch Hands with a verified skin neoplasm within the low, medium, and high current dioxin categories were 20.0, 16.5, and 9.3 percent for time of 18.6 years or less, and 25.9, 14.0, and 14.9 percent for time over 18.6 years.

Under the maximal assumption, the interaction of current dioxin and time was nonsignificant for the unadjusted analysis of Ranch Hands with a verified skin neoplasm (Table 7-3 [f]: p=0.253). Although the interaction was nonsignificant, the relative risk for time of 18.6 years or less was of borderline significance (Table 7-3 [f]: Est. RR=0.80, p=0.062) but less than 1. The relative frequencies of Ranch Hands with verified skin neoplasms within the later time since tour stratum (≤18.6 years) were 19.6, 18.4, and 9.9 percent for the low, medium, and high current dioxin categories.

TABLE 7-3.

Analysis of All Skin Neoplasms

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=489)	Low	118	22.9	0.77 (0.62,0.96)	0.014
	Medium	243	15.2		
	High	128	12.5		
b) Maximal (n=704)	Low	181	16.6	0.88 (0.75,1.02)	0.092
	Medium	344	17.7		
	High	179	12.3		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=476)	0.77 (0.61,0.97)	0.021	SUN2HR (p<0.001) ETHBACK (p=0.032)
d) Maximal (n=687)	0.92 (0.78,1.08)	0.278	AGE (p=0.031) SUN2HR (p=0.002) ETHBACK (p=0.017)

[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 7-3. (Continued)

Analysis of All Skin Neoplasms

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=489)						0.646[b]
	≤18.6	20.0 (65)	16.5 (121)	9.3 (54)	0.69 (0.48,1.01)	0.054[c]
	>18.6	25.9 (54)	14.0 (121)	14.9 (74)	0.77 (0.58,1.03)	0.083[c]
f) Maximal (n=704)						0.253[b]
	≤18.6	19.6 (102)	18.4 (179)	9.9 (81)	0.80 (0.62,1.01)	0.062[c]
	>18.6	10.3 (78)	18.7 (166)	13.3 (98)	0.96 (0.78,1.18)	0.671[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=476)			0.604[b]	SUN2HR (p<0.001)
	≤18.6	0.70 (0.48,1.02)	0.065[c]	ETHBACK (p=0.037)
	>18.6	0.80 (0.59,1.08)	0.142[c]	
h) Maximal (n=687)			0.286[b]	AGE (p=0.022)
	≤18.6	0.86 (0.67,1.10)	0.224[c]	SUN2HR (p=0.002)
	>18.6	1.02 (0.82,1.28)	0.835[c]	ETHBACK (p=0.015)

[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 7-3. (Continued)

Analysis of All Skin Neoplasms (Verified)

i1) 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	739	13.0	All Categories		0.195
Unknown	333	17.1	Unknown vs. Background	1.38 (0.97,1.98)	0.075
Low	184	16.3	Low vs. Background	1.30 (0.84,2.04)	0.242
High	179	11.7	High vs. Background	0.89 (0.54,1.47)	0.651
Total	1,435				

j1) 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	719	All Categories		0.262	AGE (p=0.138) ETHBACK (p=0.034)
Unknown	324	Unknown vs. Background	1.32 (0.92,1.91)	0.134	SUN2HR (p=0.008)
Low	180	Low vs. Background	1.39 (0.89,2.19)	0.150	LAT (p=0.135)
High	175	High vs. Background	0.93 (0.55,1.57)	0.778	
Total	1,398				

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 7-3. (Continued)

Analysis of All Skin Neoplasms (Verified and Suspected)

i2) 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	739	13.3	All Categories		0.230
Unknown	333	17.1	Unknown vs. Background	1.35 (0.95,1.93)	0.097
Low	184	16.3	Low vs. Background	1.27 (0.82,1.99)	0.285
High	179	11.7	High vs. Background	0.87 (0.53,1.44)	0.585
Total	1,435				

j2) 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	719	All Categories		0.296	AGE (p=0.144)
Unknown	324	Unknown vs. Background	1.30 (0.90,1.87)	0.162	ETHBACK (p=0.086)
Low	180	Low vs. Background	1.36 (0.87,2.14)	0.184	SUN2HR (p=0.006)
High	175	High vs. Background	0.90 (0.53,1.52)	0.694	LAT (p=0.105)
Total	1,398				

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.

Under the minimal and the maximal assumptions, the adjusted analysis of the frequency of Ranch Hands with a skin neoplasm contained nonsignificant interactions between current dioxin and time (Table 7-3 [g] and [h]: p=0.604 and p=0.286, respectively). After adjusting for covariates under the minimal assumption (i.e., skin reaction after at least 2 hours of sun exposure and ethnic background) and under the maximal assumption (i.e., age, ethnic background, skin reaction after at least 2 hours of sun exposure), two stratum-specific relative risks, which were marginally significant in the unadjusted analysis, became nonsignificant. In both cases the unadjusted and adjusted relative risks were less than 1. Under the minimal assumption, Ranch Hands with later tours displayed a marginally significant relative risk (Adj. RR=0.70, p=0.065) but, again, it was less than 1.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis of the relative frequency of participants with a verified skin neoplasm, the overall contrast of Ranch Hands with unknown, low, and high current dioxin and Comparisons with background current dioxin was nonsignificant (Table 7-3 [i1]: p=0.195). Although the overall contrast was nonsignificant, the contrast of Ranch Hands in the unknown current dioxin category with Comparisons in the background category was marginally significant (Est. RR=1.38, 95% C.I.: [0.97,1.98], p=0.075). The adjusted analysis of participants with a verified skin neoplasm also contained a nonsignificant overall contrast (Table 7-3 [j1]: p=0.262). After adjusting for age, ethnic background, skin reaction after at least 2 hours of sun exposure, and average lifetime residential latitude, the unknown versus background contrast was nonsignificant (p=0.134), as were the other two contrasts of interest ($p \geq 0.15$ for both contrasts).

The corresponding unadjusted analysis of the combination of verified and suspected skin neoplasms contained a nonsignificant overall contrast (Table 7-3 [i2]: p=0.230); the unknown versus background category contrast was again marginally significant (Est. RR=1.35, 95% C.I.: [0.95,1.93], p=0.097). An adjusted analysis that accounted for the covariates of age, skin reaction after at least 2 hours of sun exposure, ethnic background, and average lifetime residential latitude also contained a nonsignificant overall contrast (Table 7-3 [j2]: p=0.296), as well as nonsignificant Ranch Hand versus Comparison contrasts ($p > 0.15$ for each contrast).

Malignant Skin Neoplasms

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis using initial dioxin, the frequencies of Ranch Hands having a verified malignant skin neoplasm (regardless of cell type) displayed a significant relative risk, less than 1, under the minimal assumption (Table 7-4 [a]: Est. RR=0.70, p=0.014). The relative frequencies of Ranch Hands with a verified malignant skin neoplasm were 14.4, 7.8, and 7.0 percent for the low, medium, and high initial dioxin categories. In the maximal analysis using initial dioxin, the relative risk for Ranch Hands with a verified malignant skin neoplasm was nonsignificant and also less than 1 (Table 7-4 [b]: p=0.136).

In the adjusted analysis of the frequency of Ranch Hands with a malignant skin neoplasm, there was a significant interaction between initial dioxin and ionizing radiation under the minimal assumption (Table 7-4 [c]: p=0.020). To explore this interaction, results were investigated separately for those Ranch Hands who reported exposure to ionizing

TABLE 7-4.

Analysis of Malignant Skin Neoplasms

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=489)	Low	118	14.4	0.70 (0.52,0.95)	0.014
	Medium	243	7.8		
	High	128	7.0		
b) Maximal (n=704)	Low	181	8.3	0.86 (0.70,1.05)	0.136
	Medium	344	10.8		
	High	179	6.1		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=476)	0.82 (0.60,1.13)**	0.212**	INIT*XRAY (p=0.020) ETHBACK (p=0.038) SUN2HR (p=0.004) SUNRPT (p=0.021) AGE*XRAY (p=0.013)
d) Maximal (n=687)	0.88 (0.71,1.11)	0.276	ETHBACK (p=0.042) SUN2HR (p=0.021) HAIR (p=0.142) AGE*LAT (p=0.039) SUNRPT*LAT (p=0.007) SUNRPT*XRAY (p=0.016)

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

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

TABLE 7-4. (Continued)

Analysis of Malignant Skin Neoplasms

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						0.528[b]
(n=489)	≤18.6	13.8 (65)	9.9 (121)	5.6 (54)	0.61 (0.37,0.99)	0.046[c]
	>18.6	14.8 (54)	6.6 (121)	6.8 (74)	0.74 (0.50,1.12)	0.156[c]
f) Maximal						0.797[b]
(n=704)	≤18.6	8.8 (102)	2.8 (179)	3.7 (81)	0.83 (0.62,1.13)	0.241[c]
	>18.6	7.7 (78)	9.6 (166)	6.1 (98)	0.88 (0.66,1.17)	0.386[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			0.335[b]	ETHBACK (p=0.040)
(n=476)	≤18.6	0.70 (0.42,1.16)	0.167[c]	SUN2HR (p=0.008)
	>18.6	0.96 (0.63,1.47)	0.851[c]	SUNRPT (p=0.025)
				AGE*XRAY (p=0.030)
h) Maximal			0.743[b]	ETHBACK (p=0.031)
(n=687)	≤18.6	0.88 (0.63,1.22)	0.433[c]	SUN2HR (p=0.018)
	>18.6	0.95 (0.68,1.31)	0.740[c]	AGE*LAT (p=0.045)
				SUNRPT*LAT (p=0.007)
				SUNRPT*XRAY (p=0.015)

[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 7-4. (Continued)

Analysis of Malignant Skin Neoplasms (Verified)

i1) 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	739	7.4	All Categories		0.197
Unknown	333	9.9	Unknown vs. Background	1.37 (0.87,2.15)	0.174
Low	184	9.2	Low vs. Background	1.27 (0.72,2.24)	0.417
High	179	5.0	High vs. Background	0.66 (0.32,1.36)	0.258
Total	1,435				

j1) 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	718	All Categories		0.381	SUN2HR (p=0.008) SUNRPT (p=0.028)
Unknown	324	Unknown vs. Background	1.33 (0.83,2.14)	0.238	LAT (p=0.022)
Low	180	Low vs. Background	1.47 (0.81,2.65)	0.201	AGE*ETHBACK (p=0.025)
High	175	High vs. Background	0.84 (0.40,1.78)	0.657	HAIR*XRAY (p=0.039)
Total	1,397				

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 7-4. (Continued)

Analysis of Malignant Skin Neoplasms (Verified and Suspected)

i2) 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	739	7.6	All Categories		0.209
Unknown	333	9.9	Unknown vs. Background	1.34 (0.85,2.11)	0.201
Low	184	9.2	Low vs. Background	1.24 (0.70,2.19)	0.456
High	179	5.0	High vs. Background	0.65 (0.31,1.33)	0.238
Total	1,435				

j2) 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	718	All Categories		0.374	SUN2HR (p=0.006) SUNRPT (p=0.022)
Unknown	324	Unknown vs. Background	1.30 (0.81,2.09)	0.276	LAT (p=0.015)
Low	180	Low vs. Background	1.44 (0.80,2.60)	0.222	AGE*ETHBACK
High	175	High vs. Background	0.83 (0.39,1.75)	0.618	(p=0.022) HAIR*XRAY (p=0.027)
Total	1,397				

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.

radiation and those who reported no exposure to ionizing radiation (Appendix Table F-1). For those Ranch Hands who were not exposed to ionizing radiation, the relative risk was nonsignificant (p=0.984); for Ranch Hands exposed to ionizing radiation, the relative risk was significant but less than 1 (Est. RR=0.36, p=0.029). A model without the interaction between initial dioxin and ionizing radiation produced a nonsignificant relative risk (Table 7-4 [c]: p=0.212).

Under the maximal assumption, the adjusted analysis of the frequency of Ranch Hands with a malignant skin neoplasm was nonsignificant (Table 7-4 [d]: p=0.276).

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

Under the minimal assumption, the unadjusted analysis indicated that the relative risks for Ranch Hands with a verified malignant skin neoplasm were not significantly different between time since tour strata (Table 7-4 [e]: p=0.528). However, for Ranch Hands whose time since tour was 18.6 years or less, the relative risk was significant but less than 1 (Est. RR=0.61, p=0.046). For that time stratum, the relative frequencies of Ranch Hands with a malignant skin neoplasm within the low, medium, and high current dioxin categories were 13.8, 9.9, and 5.6 percent. Under the maximal assumption, the interaction between current dioxin and time was nonsignificant for the unadjusted analysis of verified malignant skin neoplasms (Table 7-4 [f]: p=0.797).

Under both the minimal and maximal assumptions, the adjusted analysis of the frequency of Ranch Hands with a malignant skin neoplasm contained a nonsignificant interaction between current dioxin and time since tour (Table 7-4 [g] and [h]: p=0.335 and p=0.743, respectively).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis for participants with a verified malignant skin neoplasm, the overall contrast of the three Ranch Hand current dioxin categories and the Comparison background current dioxin category was nonsignificant (Table 7-4 [i1]: p=0.197). The corresponding overall contrast for the combination of verified and suspected malignant skin neoplasms was also nonsignificant for the unadjusted analysis (Table 7-4 [i2]: p=0.209). The adjusted analyses for verified malignant skin neoplasms, as well as the combination of verified and suspected malignant skin neoplasms, also contained nonsignificant overall contrasts (Table 7-4 [j1] and [j2]: p=0.381 and p=0.374, respectively).

Benign Skin Neoplasms

As mentioned earlier, the statistical analyses of skin neoplasms were generally limited to non-Black participants because Blacks have a lower susceptibility to sun-induced skin cancer. An exception occurred in the statistical analysis for benign skin neoplasms. In that case, the analyses were performed separately for non-Black participants, as well as for Black and non-Black participants combined.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis using initial dioxin, the frequency of non-Black Ranch Hands with a verified benign skin neoplasm exhibited nonsignificant relative risks less than 1 under both the minimal and maximal assumptions (Table 7-5 [a1] and [b1]: p=0.635 and p=0.771).

TABLE 7-5.

Analysis of Benign Skin Neoplasms (Non-Blacks Only)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a1) Minimal (n=489)	Low	118	8.5	0.93 (0.70,1.25)	0.635
	Medium	243	7.4		
	High	128	6.3		
b1) Maximal (n=704)	Low	181	7.7	0.97 (0.79,1.20)	0.771
	Medium	344	7.0		
	High	179	6.7		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c1) Minimal (n=489)	0.93 (0.70,1.25)	0.635	- -
d1) Maximal (n=704)	0.97 (0.79,1.20)	0.771	- -

[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 7-5. (Continued)

Analysis of Benign Skin Neoplasms
(Blacks Included)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a2) Minimal (n=521)	Low	130	8.5	0.93 (0.70,1.24)	0.609
	Medium	260	7.3		
	High	131	6.1		
b2) Maximal (n=742)	Low	185	7.6	0.97 (0.79,1.20)	0.773
	Medium	371	7.0		
	High	186	6.5		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c2) Minimal (n=521)	0.93 (0.70,1.24)	0.609	- -
d2) Maximal (n=742)	0.97 (0.79,1.20)	0.773	- -

[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 7-5. (Continued)

Analysis of Benign Skin Neoplasms
(Non-Blacks Only)

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
e1) Minimal						0.985[b]
(n=489)	≤18.6	6.2 (65)	6.6 (121)	3.7 (54)	0.89 (0.52,1.51)	0.661[c]
	>18.6	11.1 (54)	7.4 (121)	9.5 (74)	0.89 (0.62,1.28)	0.541[c]
f1) Maximal						0.165[b]
(n=704)	≤18.6	9.8 (102)	5.6 (179)	6.2 (81)	0.80 (0.56,1.14)	0.220[c]
	>18.6	2.6 (78)	9.0 (166)	8.2 (98)	1.09 (0.84,1.43)	0.516[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g1) Minimal			0.985[b]	- -
(n=489)	≤18.6	0.89 (0.52,1.51)	0.661[c]	
	>18.6	0.89 (0.62,1.28)	0.541[c]	
h1) Maximal			0.165[b]	- -
(n=704)	≤18.6	0.80 (0.56,1.14)	0.220[c]	
	>18.6	1.09 (0.84,1.43)	0.516[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 7-5. (Continued)

Analysis of Benign Skin Neoplasms
(Blacks Included)

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
e2) Minimal						0.866[b]
(n=521)	≤18.6	6.9 (72)	6.3 (128)	3.7 (54)	0.85 (0.51,1.45)	0.559[c]
	>18.6	10.3 (58)	7.6 (132)	9.1 (77)	0.90 (0.63,1.29)	0.573[c]
f2) Maximal						0.154[b]
(n=742)	≤18.6	9.4 (106)	5.8 (191)	6.0 (83)	0.80 (0.55,1.14)	0.213[c]
	>18.6	2.5 (79)	8.9 (179)	7.7 (104)	1.09 (0.84,1.43)	0.498[c]

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g2) Minimal			0.866[b]	- -
(n=521)	≤18.6	0.85 (0.51,1.45)	0.559[c]	
	>18.6	0.90 (0.63,1.29)	0.573[c]	
h2) Maximal			0.154[b]	- -
(n=742)	≤18.6	0.80 (0.55,1.14)	0.213[c]	
	>18.6	1.09 (0.84,1.43)	0.498[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 7-5. (Continued)

Analysis of Benign Skin Neoplasms
(Non-Blacks Only)
(Verified)

i1) 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	739	6.0	All Categories		0.828
Unknown	333	7.2	Unknown vs. Background	1.23 (0.73,2.05)	0.437
Low	184	7.1	Low vs. Background	1.20 (0.63,2.28)	0.575
High	179	7.3	High vs. Background	1.24 (0.65,2.35)	0.516
Total	1,435				

j1) 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	738	All Categories		0.808	HAIR (p=0.120)
Unknown	333	Unknown vs. Background	1.26 (0.75,2.11)	0.384	
Low	184	Low vs. Background	1.21 (0.64,2.31)	0.555	
High	179	High vs. Background	1.21 (0.63,2.30)	0.565	
Total	1,434				

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 7-5. (Continued)

Analysis of Benign Skin Neoplasms
(Blacks Included)
(Verified)

i2) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	5.9	All Categories		0.722
Unknown	345	7.5	Unknown vs. Background	1.31 (0.80,2.16)	0.285
Low	196	7.1	Low vs. Background	1.24 (0.67,2.30)	0.500
High	187	7.0	High vs. Background	1.20 (0.64,2.27)	0.572
Total	1,514				

j2) 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		0.680	HAIR (p=0.106)
Unknown	345	Unknown vs. Background	1.35 (0.82,2.22)	0.246	
Low	196	Low vs. Background	1.25 (0.67,2.33)	0.478	
High	187	High vs. Background	1.17 (0.62,2.22)	0.621	
Total	1,513				

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.

An unadjusted analysis of verified benign skin neoplasms for Black and non-Black Ranch Hands combined produced essentially the same results as the preceding analyses (Table 7-5 [a2] and [b2]: p=0.609 and p=0.773, respectively). Under each assumption, no covariates were retained in the adjusted analysis of the non-Black Ranch Hands (Table 7-5 [c1] and [d1]), as well as the combined cohort of Black and non-Black Ranch Hands (Table 7-5 [c2] and [d2]); therefore, the unadjusted and adjusted results were the same.

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

Under both the minimal and maximal assumptions, the unadjusted analysis of verified benign skin neoplasms for non-Black Ranch Hands displayed a nonsignificant current dioxin-by-time since tour interaction (Table 7-5 [e1] and [f1]: p=0.985 and p=0.165, respectively). Combining the Black Ranch Hands with non-Black Ranch Hands also produced nonsignificant interactions (Table 7-5 [e2] and [f2]: p=0.866 and p=0.154, respectively) as well as nonsignificant relative risks within time stratum. No covariates were retained in the adjusted models for either the non-Black Ranch Hand cohort (Table 7-5 [g1] and [h1]), or after Black Ranch Hands were included in the analysis (Table 7-5 [g2] and [h2]); hence the unadjusted and adjusted results were identical.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis indicated that non-Black Ranch Hands in the unknown, low, and high current dioxin categories and non-Black Comparisons in the background current dioxin category were not significantly different with respect to the relative frequency of participants with a verified benign skin neoplasm (Table 7-5 [i1]: p=0.828). Although nonsignificant, each of the Ranch Hand versus Comparison contrasts had a relative risk over 1. Including Blacks with non-Blacks also resulted in nonsignificant overall and individual contrasts with associated relative risks greater than 1 (Table 7-5 [i2]: p=0.722).

The adjusted analysis also produced a nonsignificant overall contrast for the non-Black participants (Table 7-5 [j1]: p=0.808). An adjusted analysis performed with Black and non-Black participants combined also exhibited a nonsignificant overall contrast (Table 7-5 [j2]: p=0.680). Although nonsignificant, the relative risks for the individual contrasts were greater than 1.

Because there were no Comparisons with a suspected benign skin neoplasm, analysis of combined verified and suspected neoplasms was not performed.

Skin Neoplasms of Uncertain Behavior or Unspecified Nature

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, no Ranch Hands had a verified skin neoplasm of uncertain behavior or unspecified nature. Under the maximal assumption, only one Ranch Hand in the low initial dioxin category had this type of verified neoplasm (Table 7-6 [a] and [b]). Due to such sparse data, unadjusted and adjusted analyses were not performed.

TABLE 7-6.

Analysis of Skin Neoplasms of Uncertain Behavior or Unspecified Nature

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)	p-Value
a) Minimal (n=489)	Low	118	0.0	--	--
	Medium	243	0.0		
	High	128	0.0		
b) Maximal (n=704)	Low	181	0.6	--	--
	Medium	344	0.0		
	High	179	0.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) Minimal (n=489)	--	--	--
d) Maximal (n=704)	--	--	--

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

TABLE 7-6. (Continued)

Analysis of Skin Neoplasms of Uncertain Behavior or Unspecified Nature

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
e) Minimal						- -
(n=489)	≤18.6	0.0 (65)	0.0 (121)	0.0 (54)	- -	- -
	>18.6	0.0 (54)	0.0 (121)	0.0 (74)	- -	- -
f) Maximal						- -
(n=704)	≤18.6	1.0 (102)	0.0 (179)	0.0 (81)	- -	- -
	>18.6	0.0 (78)	0.0 (166)	0.0 (98)	- -	- -

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

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
g) Minimal			- -	- -
(n=489)	≤18.6	- -	- -	
	>18.6	- -	- -	
h) Maximal			- -	- -
(n=704)	≤18.6	- -	- -	
	>18.6	- -	- -	

--: Relative risk/confidence interval/p-value not given due to the sparse number of abnormalities; adjusted analysis not performed 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 7-6. (Continued)

Analysis of Skin Neoplasms of Uncertain Behavior or Unspecified Nature (Verified)

i1) 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	739	0.0	All Categories		--
Unknown	333	0.3	Unknown vs. Background	--	0.622
Low	184	0.0	Low vs. Background	--	--
High	179	0.0	High vs. Background	--	--
Total	1,435				

j1) 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	739	All Categories		--	--
Unknown	333	Unknown vs. Background	--	--	
Low	184	Low vs. Background	--	--	
High	179	High vs. Background	--	--	
Total	1,435				

--: Relative risk/confidence interval/p-value not given due to the sparse number of abnormalities; adjusted analysis not performed due to the sparse number 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 7-6. (Continued)

Analysis of Skin Neoplasms of Uncertain Behavior or Unspecified Nature (Verified and Suspected)

i2) 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	739	0.1	All Categories		--
Unknown	333	0.3	Unknown vs. Background	2.22 (0.14,35.65)	0.999
Low	184	0.0	Low vs. Background	--	0.999
High	179	0.0	High vs. Background	--	0.999
Total	1,435				

j2) 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	739	All Categories		--	--
Unknown	333	Unknown vs. Background	--	--	
Low	184	Low vs. Background	--	--	
High	179	High vs. Background	--	--	
Total	1,435				

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

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

Due to sparse data, unadjusted and adjusted analyses were not performed (Table 7-6 [e] and [f]).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

With respect to the categorized current dioxin analysis, the one Ranch Hand with a verified skin neoplasm of uncertain behavior or unspecified nature was in the unknown current dioxin category (Table 7-6 [i1]). Because of the sparse number of neoplasms, only the contrast of the unknown category versus the background category was performed; it was found to be nonsignificant (p=0.622). For the combination of verified and suspected skin neoplasms, one Comparison had a suspected skin neoplasm of uncertain behavior or unspecified nature (Table 7-6 [i2]). The contrasts of interest were nonsignificant (p=0.999 for each contrast). Adjusted analyses were not performed due to the sparse number of neoplasms.

Basal Cell Carcinoma—All Sites and by Location/Site

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the unadjusted analysis of the frequency of Ranch Hands with a verified basal cell carcinoma at any site contained a significant relative risk less than 1 with respect to initial dioxin (Table 7-7 [a1]: Est. RR=0.73, p=0.037). The relative frequencies were 11.0, 7.4, and 5.5 percent for the low, medium, and high initial dioxin categories. The corresponding analysis under the maximal assumption was nonsignificant (Table 7-7 [b1]: p=0.114). Under the minimal assumption, the adjusted analysis of verified basal cell carcinoma produced a nonsignificant relative risk less than 1 (Table 7-7 [c1]: p=0.317) after adjusting for the two skin reaction to sun exposure covariates, ethnic background, and an interaction between age and ionizing radiation. Under the maximal assumption, the adjusted analysis also was nonsignificant for an association with initial dioxin (Table 7-7 [d1]: p=0.449).

Under both assumptions of the unadjusted analysis, the relative risk of the frequency of Ranch Hands with a verified basal cell carcinoma on the ear, face, head, and neck was significant but less than 1 (Table 7-7 [a2] and [b2]: Est. RR=0.51, p=0.002 and Est. RR=0.71, p=0.017, respectively). In the minimal analysis, the relative frequencies were 8.5, 4.9, and 1.6 percent for the low, medium, and high initial dioxin categories. The corresponding relative frequencies for the maximal analysis were 5.5, 6.4, and 1.7 percent. The covariates of age, skin reaction after at least 2 hours of sun exposure, and ethnic background were retained in the adjusted model. Under the minimal assumption, the relative risk remained significant but less than 1 (Table 7-7 [c2]: Adj. RR=0.59, p=0.025). Under the maximal assumption, the relative risk became marginally significant and also remained less than 1 (Table 7-7 [d2]: Adj. RR=0.77, p=0.087).

Under the minimal and maximal assumptions, the unadjusted analyses using initial dioxin contained nonsignificant relative risks that were equal to or less than 1 for verified basal cell carcinoma on the trunk (Table 7-7 [a3] and [b3]: p=0.632 and p=0.999, respectively). The adjusted analyses produced relative risks slightly greater than 1 but they were nonsignificant (Table 7-7 [c3] and [d3]: p=0.954 and p=0.684).

TABLE 7-7.

Analysis of Basal Cell Carcinoma (All Sites Combined)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a1) Minimal (n=489)	Low	118	11.0	0.73 (0.53,1.00)	0.037
	Medium	243	7.4		
	High	128	5.5		
b1) Maximal (n=704)	Low	181	8.3	0.84 (0.68,1.05)	0.114
	Medium	344	9.0		
	High	179	5.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c1) Minimal (n=476)	0.85 (0.60,1.18)	0.317	ETHBACK (p=0.073) SUN2HR (p=0.063) SUNRPT (p=0.029) AGE*XRAY (p=0.024)
d) Maximal (n=687)	0.92 (0.72,1.16)	0.449	ETHBACK (p=0.046) SUN2HR (p=0.068) SUNRPT (p=0.017) AGE*XRAY (p=0.045)

[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 7-7. (Continued)

Analysis of Basal Cell Carcinoma
(Ear, Face, Head, and Neck)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a2) Minimal (n=489)	Low	118	8.5	0.51 (0.31,0.83)	0.002
	Medium	243	4.9		
	High	128	1.6		
b2) Maximal (n=704)	Low	181	5.5	0.71 (0.53,0.96)	0.017
	Medium	344	6.4		
	High	179	1.7		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c2) Minimal (n=476)	0.59 (0.36,0.98)	0.025	AGE (p=0.077) SUN2HR (p=0.003) ETHBACK (p=0.125)
d2) Maximal (n=687)	0.77 (0.56,1.05)	0.087	AGE (p=0.011) SUN2HR (p=0.001) ETHBACK (p=0.092)

[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.