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Epidemiologic Study to Determine Possible Adverse Effects to Rocketdyne/Atomics International Workers from Exposure to Ionizing Radiation

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EXECUTIVE SUMMARY

Background and Objective. In the early 1990s, a worker health study—discussed in this report—was initiated in response to strong concerns voiced by area residents about the use of radioactive and toxic substances at the Santa Susana Field Laboratory (SSFL) of Rocketdyne/Atomics International (AI), a Department of Energy contractor. Starting in the early 1950s, SSFL activities included the operation of nuclear reactors, handling of plutonium, and rocket-engine testing. This report will focus on the possible effects of exposures to two types of ionizing radiation on cancer mortality among Rocketdyne/AI workers: penetration of the body by gamma and X rays (external radiation); and the ingestion, inhalation, or absorption of alpha-emitting radionuclides such as uranium (internal radiation). Possible effects of selected chemical exposures on cancer mortality will be addressed in a future addendum report.

Health effects of radiation have been widely studied among nuclear workers in the past two decades, but much controversy remains concerning the extent to which chronic exposure to low-level ionizing radiation encountered in the workplace increases the risk of specific cancers. Despite the biologic plausibility of carcinogenic effects on several ("radiosensitive") organs and tissues, the results for most types of cancers are rather inconsistent across studies. The only type of cancer that has been found in most studies to be associated with occupational radiation exposures is leukemia.

Methods. We conducted a retrospective cohort study among employees of Rocketdyne/AI, who were monitored for low-level ionizing-radiation exposure between 1950 and 1993. The study population consisted of 4,563 employees monitored for external radiation and 2,297 employees monitored for internal radiation, with the second group being mostly a subset of the first.

Historical radiation information was abstracted from company records and used to measure cumulative doses (in millisieverts [mSv]) of both types of radiation. (The radiation dose
from one chest x-ray, for example, is approximately 0.1 mSv.) Personnel records provided us with information about age, gender, employment history, pay type (salaried professional/managerial, salaried technical/administrative, or hourly), and some limited information on work location. Crude measures of asbestos and monomethyl-hydrazine exposures were based on job titles during selected periods of employment and, for asbestos, on selected work locations. Medical records allowed us to obtain smoking information for a subset of our cohort. Three sources of vital-status information plus Rocketdyne/AI beneficiary files were used to identify deaths occurring by December 31, 1994. We collected information about underlying and contributing causes of death from death certificates obtained for deceased cohort members.

Two analytic approaches were used in this study for different purposes: internal comparisons of monitored workers according to measured level of cumulative radiation dose (dose-response analyses); and external comparisons of monitored Rocketdyne/AI workers with two other (external) reference populations. We relied on the internal comparisons to estimate radiation effects in this study. External comparisons were used solely to describe the study population, to assess the net influence of "healthy-worker" effects operating in this study population, and to identify types of cancers with elevated mortality rates that might be explained by radiation (or other) effects estimated from the internal comparisons.

In the internal-comparison approach, conditional logistic regression was used to estimate the effects (rate ratios) of external- and internal-radiation exposures on cancer mortality among monitored workers. Externally monitored workers were used to estimate the effects of external radiation, and internally monitored workers were used to estimate the effects of internal radiation. Cumulative (total) radiation doses were treated as time-dependent predictors and lagged by zero to 20 years to account for varying periods of induction/latency. To estimate each radiation effect, we controlled analytically for the other type of radiation exposure (internal or external dose), age at risk (time dependent), time since first radiation monitoring (time dependent), pay type, and in
certain analyses, other variables such as asbestos and hydrazine exposures.

Because there were not enough deaths from most specific cancer sites to conduct separate dose-response analyses, we grouped cancers on the basis of a priori information. For analyses of the effects of external radiation, the outcome events of interest were deaths from all cancers, solid cancers of "radiosensitive" organs (according to BEIR V, 1990), hemato- and lymphopoietic cancers (blood and lymph system, excluding chronic lymphocytic leukemia), and lung cancer (the most common radiosensitive solid cancer). In analyses of the effects of internal radiation, the outcome events of interest were deaths from all cancers, hemato- and lymphopoietic cancers (excluding chronic lymphocytic leukemia), lung cancer, upper-aerodigestive-tract cancers (oral cavity, pharynx, esophagus, and stomach), and urinary-tract cancers (bladder and kidneys).

Since the results of other occupational studies suggest that the effect of low-level radiation may depend on the ages at which workers are exposed, we used several methods to examine possible interaction effects between radiation dose and age at exposure. The principal method was to estimate simultaneously the separate effects of cumulative radiation dose received during three age intervals: before age 40, between ages 40 and 49, and after age 49.

In the external-comparison approach, we estimated standardized mortality ratios (SMRs), comparing the mortality experience of monitored Rocketdyne/AI workers with the mortality experience of two external populations: the general U.S. population, and a population of workers assembled by the National Institute for Occupational Safety and Health (NIOSH) from other occupational studies. SMRs were based on stratification by age, sex, and calendar year; in addition, comparisons with the NIOSH population were stratified by pay type (salaried vs. hourly).

**Results.** Among externally monitored workers, we identified 875 total deaths, of which 258 (29.5%) were due to cancer as the underlying cause. Among internally monitored workers, we identified 441 total deaths, of which 134 (30.4%) were due to cancer as the underlying cause. By
comparing different sources of vital-status information, we established that the identification of
deaths before 1995 was nearly complete.

In the dose-response analyses of monitored workers, external-radiation dose was positively
associated with the rate of dying from hemato- and lymphopoietic cancers and from lung cancer;
the mortality rates for both types of cancer were especially elevated for dose levels greater than 200
mSv. We also observed increasing trends in mortality rates with increasing external-radiation dose
for all cancers and for radiosensitive solid cancers. No external-radiation effects were observed for
cancers of nonradiosensitive organs.

Among workers monitored for internal radiation, we found increasing trends in mortality
rates with increasing internal-radiation dose for upper-aerodigestive-tract cancers and for hemato-
and lymphopoietic cancers. No appreciable internal-radiation effects were observed for cancers of
the lung or urinary tract.

The estimated external- and internal-radiation effects did not change when adjusting for
our measures of asbestos and hydrazine exposures. Furthermore, smoking status was not
systematically associated with cumulative external-radiation dose in three subgroups of monitored
workers sampled at different times.

Our analyses of external-radiation effects at different ages of exposure yielded contrasting
results for different cancer outcomes. For total cancers, radiosensitive solid cancers and lung
cancer, we found that the effect of external radiation was relatively greater for doses received after
age 50; but for hemato- and lymphopoietic cancers, we found the effect was relatively greater for
doses received before age 50.

Compared with the general U.S. population, Rocketdyne/AI workers monitored for
external- or internal-radiation exposure experienced lower mortality rates from all causes, all
cancers, and heart disease. Comparisons of monitored Rocketdyne/AI workers with NIOSH-cohort
members of comparable pay type showed lower mortality rates for all causes and heart disease, but
similar mortality rates for total cancers. Compared with either reference population, monitored Rocketdyne/AI workers also experienced a higher mortality rate from leukemias.

Conclusions. All available evidence from this study indicates that occupational exposure to ionizing radiation among nuclear workers at Rocketdyne/AI has increased the risk of dying from cancers of the blood and lymph system. Despite the small numbers of deaths from these cancers in workers with relatively high doses, we observed associations for both external and internal radiation, and these associations are not likely to be chance findings; furthermore, these findings are consistent with the results of our external comparisons with two reference populations. In addition, these findings are consistent with results previously reported for several other nuclear cohorts.

Exposure to external radiation appears to have increased the risk of dying from lung cancer. Although this effect has not been observed consistently in other studies of nuclear workers, it does not appear to be due to the confounding effects of smoking, asbestos, or hydrazine exposures. Nevertheless, we cannot rule out residual confounding by these factors or by unmeasured risk factors such as other chemical carcinogens, but such potential bias could be in either direction.

Results of this study strongly suggest that exposure to internal radiation has increased the risk of dying from cancers of the upper-aerodigestive tract. We observed a strong dose-response relationship that is not likely to be a chance finding. Although there were limitations in measuring internal-radiation doses among workers, we would expect such measurement errors to result in an effect estimate that is smaller than the true effect (i.e., bias toward the null). Nevertheless, we cannot rule out confounding (in either direction) by alcohol consumption, dietary factors, and other unmeasured risk factors. Upper-aerodigestive-tract cancers have not been analyzed as a single group in previous radiation studies, and we did not have enough deaths of each cancer type in this
group to conduct separate dose-response analyses; thus, our finding needs to be replicated in other populations. In contrast to findings reported for several other epidemiologic studies of radiation effects, we observed an association between cumulative external-radiation dose and total-cancer mortality. Indeed, the estimated excess rate ratio (rate ratio minus one) corresponding to the effect of 100 mSv was at least 6 to 8 times greater in our study than comparable estimates extrapolated from the study of A-bomb survivors. Our results, however, are consistent with those of two previous studies of nuclear workers.

We estimated that 9 cancer deaths observed in the externally monitored cohort were attributable to external-radiation doses of 10 mSv or more; this attributable number represents 3.5% of all observed cancer deaths and 11.1% of "exposed" cancer deaths with cumulative doses of 10 mSv or more. We also estimated that 15 cancer deaths observed in the internally monitored cohort were attributable to internal-radiation doses greater than 0 mSv; this attributable number represents 11.2% of all observed cancer deaths and 27.3% of "exposed" cancer deaths with cumulative doses greater than 0 mSv. Since we were not able to provide confidence limits for these estimates, their precision cannot be assessed. Nevertheless, the estimated numbers of attributable deaths may be conservative for several reasons: e.g., they ignore deaths possibly due to external doses less than 10 mSv; they ignore possible radiation-induced cancer deaths after 1994; and they ignore radiation-induced cases of cancer that are not fatal.

The results of this study also suggest that the effect of low-level ionizing radiation may vary by age at exposure and that the pattern of this effect modification by exposure age may differ by type of cancer. While the estimated effects of external radiation on total cancers, radiosensitive solid cancers, and lung cancer were largest for doses received after age 50, the estimated effect on hemato- and lymphopoietic cancers was largest for doses received before age 50. Despite the low statistical power for testing the effects of age-specific radiation doses in our analyses, these results are consistent with findings from other studies. We therefore recommend that other researchers
consider exposure age when estimating the effects of ionizing radiation.

Results of the external comparisons suggest that the mortality rates for all causes and, in particular, heart disease were lower for monitored Rocketdyne/AI workers than for either the general U.S. population or the NIOSH population of other worker cohorts. These findings do not mean that being employed at Rocketdyne/AI decreases the risk of dying from heart disease or other causes, but rather that healthier individuals are more likely to get employed at Rocketdyne/AI and stay in the radiation-monitoring program than are less healthy individuals. This latter phenomenon is known as the "healthy-worker effect."

Although we cannot rule out all forms of error in our estimates of radiation effects, we believe the direction of possible bias is no more likely to be away from the null (exaggerating effects) than toward the null (underestimating effects). Moreover, the positive findings observed in our study, in contrast to many previous studies, may be due in part to the extended follow-up period. Longer follow-up allows time for the development of radiation-induced cancers that are characterized by long induction/latency periods or that tend to occur more frequently after exposures late in life. It should be noted that only 20% of monitored workers had died by the end of the follow-up period. On the basis of this consideration, plus other methodologic issues that cannot be resolved by the present study, we recommend continued follow-up of the Rocketdyne/AI cohort in the coming decades. Future surveillance should include the detection of cancer incidence as well as mortality.
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1. INTRODUCTION

This report describes the statistical associations observed between occupational exposure to low-level ionizing radiation and cancer mortality among workers employed since 1950 at the Santa Susana Field Laboratory (SSFL) and related facilities in the Los Angeles area. These facilities, including the field station, have formed the basis of what is now the Rocketdyne Division of Boeing North America, Inc. Nuclear operations at the field station have long been a focus of concern in the community. More than 15 years ago, workers and local residents began raising questions about accidents at the facility and the risk of radioactive releases that might prove harmful to SSFL personnel or residents in the surrounding area.

The Study Setting: Rocketdyne/Atomics International

The Santa Susana Field Laboratory, located in the Simi Hills of Ventura County adjacent to the Los Angeles County line, was established in 1948 by North American Aviation (NAA), the predecessor to Rockwell International, which recently sold the facility to Boeing North America, Inc. Although it was initially engaged in rocket-engine testing alone, the SSFL branched out into nuclear-power operations in 1956. Those nuclear programs had been developed earlier in the decade at a Downey plant housing the NAA division, soon to be called Atomics International (AI). In 1955, AI established headquarters at Canoga Park and transferred its nuclear-reactor development and testing programs to Area IV of the SSFL. Since then, Area IV has been the site of 10 nuclear reactors and a variety of other radiation-generating projects. In addition, at the end of the 1950s, AI built a new complex on De Soto Avenue, not far from the Canoga Park headquarters, with nuclear work at the new facility focusing on fuel production and fuel-rod assembly.

In 1984, AI merged with Rocketdyne, which had been the rocket-propulsion division at NAA and later at Rockwell and Boeing. For purposes of this report, we will use the term...
"Rocketdyne/AI" to refer to the combination of entities that fed into the present-day Rocketdyne, including the nuclear operations at Downey, the SSFL, and the Canoga and De Soto facilities. Exposures to ionizing radiation at Rocketdyne/AI have taken two forms. The most common form of exposure has been external exposures, which entail penetration of the body by gamma rays, X rays, or neutrons. Most external exposures are characterized as low linear-energy-transfer (LET) radiation. Internal exposures, in contrast, depend on deposition of high linear-energy-transfer particles within the body as the result of ingestion, inhalation, or absorption through wounds. Alpha-emitting radionuclides such as uranium have been responsible for the majority of internal exposures at Rocketdyne/AI.

The major sources of external radiation exposure were concentrated at the SSFL (Area IV), with the preponderance of activity involving the nuclear reactors functioning from 1957 through the 1970s. Radioactivity was not only released from operation of the reactors, but it was also associated with criticality testing, the manufacture of reactor-fuel assemblies, disassembly of reactors and used-fuel assemblies, small-scale laboratory research, and storage of radioactive material. Substantial external exposures to radiation also occurred early in the 1950s at the NAA Downey plant, where California's first nuclear reactor was designed, constructed, and operated. Limited exposures were associated with a reactor at the central Canoga Park facility.

Internal exposures resulted from operations performed at the De Soto facility and the SSFL and involved the use of radionuclides such as uranium-238 and plutonium-239. Activities with the potential for exposing employees internally to radionuclides included glove box operations, used for handling nuclear fuel, which were conducted during the periods, 1962-68 and 1973-82.

Nuclear operations were phased out between the mid-1960s and the early 1980s, when the last reactor was shut down. However, decladding of irradiated reactor fuel continued at the SSFL between 1975 and 1987. Since then, the potential for radiation exposure at Rocketdyne/AI has been limited to personnel employed in decontamination and decommissioning of the nuclear facilities,
storage of radioactive material, industrial radiography, and applied physics experimentation.

History of the Study

Public awareness of Rocketdyne/Al's nuclear programs was raised in 1980 by media coverage of a community-activist report describing accidents at SSFL that involved known or potential releases of radioactivity (Committee to Bridge the Gap, 1980). During the subsequent decade, concerned workers and residents mobilized support for an investigation to determine whether harmful health effects were occurring at SSFL's nuclear sites or in the adjacent community. As a result, in 1990, several members of the California State Assembly asked the California Department of Health Services (CDHS) to undertake such an investigation.

In response, CDHS conducted preliminary statistical analyses of newly diagnosed cancer cases in the Los Angeles County census tracts immediately adjacent to SSFL for the years 1978-88, and in the tracts on both the Los Angeles and Ventura County sides for the years 1988-1989. These studies suggested a higher-than-expected incidence of bladder cancers among Los Angeles County residents living near SSFL during the period 1983-88. In a comparison of the proportions of different types of cancer diagnosed in 1988-89 among Los Angeles and Ventura County residents living near SSFL, relative to the proportions reported for all other residents of the same counties, the proportional incidence of bladder cancer was again somewhat elevated for people living at the Los Angeles boundary, but somewhat depressed for those at the Ventura boundary. On the other hand, men living near the SSFL in Ventura County had a higher proportion of lung cancer than did men living elsewhere in the county, but women did not, nor did either men or women living near the site in Los Angeles County. Leukemias and other cancers believed to be most sensitive to external radiation were not found to occur with unusual frequency in the communities surrounding the SSFL in any of the periods examined. It is possible, however, that the effects of radioactivity releases from SSFL may not be limited to leukemias or other "radiosensitive" cancers.
Because of the lack of consistency in these findings, the absence of information about the extent to which residents may have been exposed to contaminants released at the SSFL, and other limitations and uncertainties, the community studies remain difficult to interpret. The two cancers that appeared to be excessive in some localities, those of the bladder and the lung, are strongly associated with risk factors other than radiation, especially smoking and occupational exposure to certain chemicals.

Thus, the CDHS analyses underscored the importance of conducting a study of the effects of both chemical and radiation exposures in the cohort of nuclear workers at SSFL and its associated facilities. This population is well-defined and was exposed earliest and most extensively to Rocketdyne/Al's radiation and to various potentially carcinogenic chemicals. Historical records dating to the beginning of the 1950s are available to document vital status and causes of death for the entire population, as well as to provide at least qualitative indicators of exposure to broad classes of chemicals and quantitative measures of individual radiation doses.

In 1991, the state legislators who had intervened in support of community concerns were able to secure funding from the U.S. Department of Energy for the epidemiologic study of workers reported here.

Background: Findings From Other Epidemiologic Studies

A number of previous studies have examined the cancer mortality associated with long-term exposure to low-level ionizing radiation, which is characteristic of occupational settings. (As used in this report, "exposure" refers to a situation in which radiation or radioactivity is in the immediate environment of a person.) Few consistent patterns have emerged, however, and the carcinogenic potential of the doses resulting from such exposures remains controversial. (As used in this report, "dose" means absorbed dose—i.e., energy absorbed in tissue divided by the mass of that tissue.)

Traditional radiobiologic theory suggests that the fractionated doses (doses delivered
during several distinct exposures) of gamma and X rays produced by most occupational and diagnostic radiation exposures should be less harmful than the same dose delivered in a single exposure. Greater fractionation allows greater time for damage from one exposure to be repaired before a second exposure occurs, and in many cases will lead to a lower probability of effect for the same total dose (BEIR V, 1990). The exception appears to be high linear-energy-transfer (LET) radiation such as from radon or radium, where an inverse dose-rate effect has been noted; that is, spreading the same dose over longer periods of time appears to increase the probability of cancer above that from doses delivered during a single, rapid exposure (United Nations, 1994; BEIR IV, 1988).

Among A-bomb survivors, it is not clear whether single whole-body doses of less than 200 milligray (mGy) (20 rads) have increased the risk of cancer (Shimizu et al., 1990; see Table 1.1). Using a linear no-threshold model (i.e., assuming all doses increase the probability of cancer and this probability is directly proportional to dose) to extrapolate from the data on the survivors receiving doses above 200 mGy to doses below this level yields an estimate of the probability of cancer, excluding leukemias, equal to 0.41% (90% confidence interval [CI] 0.32-0.52%) per 10 mGy (per rad). It should be noted that these exposures involved doses to the entire body. However, studies of low-dose external exposures among nuclear workers, conducted over the past 20 years have not yielded unequivocal results (Stewart and Kneale, 1991). In these studies, estimates of the excess relative risk of cancer per 10 mGy have ranged from 0% to 4.94%, depending on characteristics of the cohort studied, the models used to estimate risk, and assumptions about the time that must elapse between the dose and the appearance of the cancer if the latter is to be attributed to the former (i.e., the "lag" period) (Gribbin et al., 1993; Wing et al., 1993; Fraser et al., 1993). Thus, the results obtained from some nuclear-worker cohort studies raise the possibility that risk estimates for total cancers extrapolated from the A-bomb survivor data might underestimate the carcinogenic effect of doses delivered by low-level external exposure to radiation by as much as
10-fold. On the other hand, some occupational results are also consistent with the hypothesis of no effect at the doses and dose rates studied (see also Tables 1.2 and 4.2).

Similar issues of inconsistent findings have plagued attempts to estimate the effects of doses from low-level exposure to internal radioactivity (i.e., radioactivity that emits radiation within the body). In animal experiments, high doses from alpha- and beta/gamma-emitting radionuclides have resulted in immunosuppressive and carcinogenic effects to the organs in which these radionuclides concentrate (ICRP, 1980). The carcinogenic potential of such radionuclides has been confirmed in heavily exposed human populations, including uranium miners and millers, radium-dial painters, and patients treated with Thorotrast and radium-224 (Mays, 1988; BEIR IV, 1988). The cancer sites implicated coincided well with distribution patterns for the radionuclides within the body, with increases in the incidence of lung, liver, and head-sinus carcinomas, as well as leukemias and bone sarcomas. These human populations have experienced carcinogenic effects of internal radiation when high doses are delivered, specifically when the dose equivalent (the product of the dose and a quality factor) is greater than 1 sievert (Sv) (100 rem) in an irradiated organ.

Studies have been conducted recently to examine the effects of internally deposited radionuclides on the health of employees in the nuclear industry. Dose equivalents of less than 1 Sv have been associated with internal exposure to predominantly alpha-emitting radionuclides. In one such investigation, 26 white male workers who had been exposed to airborne plutonium during World War II were followed for 42 years, to 1986 (Voelz and Lawrence, 1991). At that time, the mean age of the study population was 66 years. By 1990, 7 subjects had died; three were diagnosed with lung cancer, one with osteosarcoma, and another with fatal chronic respiratory disease. The individual who died from osteosarcoma had received an estimated average skeletal dose equivalent of 16 millisievert (mSv) before his death. In contrast, the lowest average skeletal dose received by individuals who died of bone sarcomas in the earlier radium-dial painter studies was 800 mSv.

The results of selected occupational cohort studies from the nuclear industry have included
increased mortality of lung cancer among workers exposed to uranium or plutonium (Wiggs et al., 1994; Checkoway et al., 1988); increased mortality of lung and hemato- and lymphopoietic cancers among workers exposed to plutonium (Wilkinson et al., 1987); and increased incidence and mortality of prostate cancers among employees exposed to tritium (Beral et al., 1985; 1988; Fraser et al., 1993). However, these studies have not been conclusive with respect to the carcinogenic effects of moderate-to-low doses; they have not yielded consistent results for specific types of cancers, nor do they clearly indicate what cancers are affected by radiation; and most studies were based on small numbers of outcome events (resulting in imprecise estimates of effect). Moreover, some of the reported associations were not confirmed when the follow-up period was extended (Dupree et al., 1994).

In a pooled analysis of data from 7 occupational cohort studies, Cardis et al. (1995) reported that the only excess risk of cancer mortality for workers exposed to external radiation was for leukemias, excluding chronic lymphocytic leukemia. The estimated rate ratio for a cumulative dose of 100 mSv was 1.22 (95% CI 0.94-1.58), which is similar to the effect estimate reported in BEIR V (1990) for A-bomb survivors (see Table 4.2). Although Cardis et al. conclude that the effect of radiation on leukemias did not differ "significantly" across studies, their results clearly show substantial heterogeneity; the estimated rate ratio for 100 mSv ranged from 0.9 to 5.8.

Inconsistencies across studies in the observed effects of internal and external radiation exposure might be due to several factors: random (sampling) error, selection biases resulting from healthy-worker effects, and interstudy differences in duration of follow-up, lag-period assumptions, types of radiation, dosimetry, dose distributions, measurement error, residual confounding, and the distribution of effect modifiers. The present study represents one of the smallest nuclear-industry cohorts studied, but it has one of the longest follow-up periods reported in the literature. We have also incorporated methods to deal with healthy-worker effects, varying induction/latency (lag) periods between radiation exposure and cancer death, and possible interaction effects between
radiation and other risk factors. Thus, our study should add to the growing body of information about the effects of prolonged, low-level exposure to radiation in the workplace.

Objectives

The objective of this study was to determine whether workers at Rocketdyne/Al's nuclear sites have experienced excessive mortality from specific cancers, total cancers, or other causes as a result of their work-related exposures to radiation or chemical carcinogens. By examining dose-response associations for a range of cumulative external and internal radiation dose levels, we will assess whether our data support the relative excess-risk extrapolations derived from high-dose studies of A-bomb survivors, or whether they are consistent with results from other occupational cohort studies (see Table 4.2). We will also address the hypothesis that the effect of radiation dose on cancer mortality varies with age at exposure.

Unfortunately, information about chemical exposures proved to be extremely elusive, with almost no quantitative measures having been retained in currently available Rocketdyne files. As a result, it has been possible to define only crude groupings of workers whose job titles and periods of employment placed them at increased risk of exposure to some types of chemicals and chemical combinations such as asbestos and hydrazine. The process of classifying and analyzing these complex chemical exposures for a larger group of workers is still ongoing (see the last part of Section 2 for a brief description of this process). This report will therefore focus on the radiation component of the study; chemical exposures will be considered only as potential confounders of radiation effects. The possible effects of chemical exposures in the workplace will be addressed in a future addendum report.

2. METHODS

Study Design
We drew on the population of all those employed by Rocketdyne/AI since 1950–55,000 total registered in the company's personnel files—to carry out a worker mortality study with a retrospective (historical) cohort design. The record systems required for such a study were provided mainly by Rockwell International Corporation. Personnel and radiation-monitoring records from 1950 through 1993 allowed us to define the subpopulations of interest and to obtain data on their radiation doses and other personal risk factors such as age. Death certificates retrieved from Rocketdyne/AI pension files and state vital-statistics offices enabled us to analyze the relationship between exposure status and mortality rates from various causes.

For the portion of the study described in this report, we restricted our analyses to the 5,066 Rocketdyne/AI nuclear workers enrolled in the company's Health Physics Radiation Monitoring Program between January 1, 1950 and December 31, 1993. In a future addendum to this report, we will examine mortality patterns for a larger group of workers employed in certain jobs and periods associated with exposure to selected chemicals such as asbestos and hydrazine. These carcinogenic substances were commonly used in nuclear and other Rocketdyne/AI operations and might have increased the risk of cancer mortality in these workers.

Subject Selection

In restricting our analyses of radiation effects to workers monitored in the Health Physics Radiation Monitoring Program (HPRMP), we assumed that these employees were subject to similar self-selection and company-selection procedures and, therefore, should be relatively comparable with respect to baseline health status. Some employees who were never enrolled in the HPRMP were occasionally badged or monitored for radionuclides as a result of temporary assignment to areas with potential for radiation exposure. Since these employees might not have met the same baseline health criteria, they were not included in our study cohort.

The HPRMP cohort included workers monitored for both external and internal radiation.
For our analyses, we divided it into two partially overlapping subsets. The first subset consisted of the 4,665 HPRMP enrollees who had been monitored for external-radiation exposure at least once during their employment at Rocketdyne/AI. Thus, the other 401 members of the total HPRMP cohort were not included in this "externally monitored group," since those individuals never received a badge, and it was impossible to determine whether they had or had not been exposed to radiation. Similarly, 2,336 employees who were ever monitored for internal-radiation exposure constituted the second, "internally monitored group," which excluded 2,730 HPRMP members who had never undergone testing for internal exposure. There was no way to determine whether those workers without monitoring records had, in fact, been unexposed. The number of HPRMP members tested for internal exposure to radionuclides peaked in 1963-64.

Not all HPRMP members were included in either of our two study groups. Specifically, 323 workers enrolled in the HPRMP had no record of ever having been monitored for either external- or internal-radiation exposures. In addition, 102 individuals (2.2%) from the externally monitored group and 39 (1.7%) from the internally monitored group had to be excluded because their company personnel records were not retrievable and their radiation records lacked birth dates and social security numbers. As a result, it was impossible to obtain vital-status information for these employees. We did not restrict the cohort based on employment duration, race, or gender.

Tables 2.1-2.6 describe the characteristics of the two final study populations. Thus, in this report we will explore the effect of external and internal radiation exposures for 4,563 externally monitored workers with known vital status and for 2,297 internally monitored workers with known vital status who were monitored at least once during their employment at Rocketdyne/AI. Note that most of the internally monitored workers (2,253) are included in the externally monitored group.

Follow-up for each eligible cohort member began at the first date of either external or internal monitoring, depending on the type of radiation exposure under investigation, or on
January 1, 1950, whichever date was later. Follow-up ended either on the date of death of a cohort member or on December 31, 1994, whichever date came first.

Data from Personnel Records

Personnel records provided us with personal identifiers and information about employment history, including the assigned division or department, location code, job title, and pay type (salaried professional/managerial, salaried technical/administrative, or hourly). In addition, a remark field on the record indicated periods of medical and other types of leave, dates of lay-off and retirement, and shift classification.

We received no information that would allow us to interpret department codes and functions consistently over time, with codes dating back to the 1950s and 1960s being especially problematic. Work-location codes for the SSFL, De Soto, and Canoga facilities of Rocketdyne/Al were very crude and did not reflect actual work sites, but rather time-clock locations. For example, at the SSFL, the only code used on personnel cardexes prior to 1960 was an "S," indicating simply SSFL. From about 1960 to 1971, 31 two-letter codes were used to refer to specific SSFL buildings; after 1971, these were replaced by 35 three-letter building codes. Since the SSFL has about 400 buildings, however, most of these buildings are not represented by these location codes. Furthermore, two time-clock buildings at the SSFL seem to be all that are listed on the majority of records, giving little indication of where the employees actually worked.

Furthermore, pay-code information before 1972 did not always correctly distinguish salaried technical/administrative personnel (also called "salaried weekly evaluated") from those paid on an hourly basis. We learned that this discrepancy was partly due to the fact that unions had not been established for certain job categories before this time and that, in general, the salaried-weekly-evaluated pay code had been used ambiguously by the personnel administration. Thus, we used job-title information for all individuals with ambiguous pay codes to determine...
whether these employees belonged to the hourly or salaried category. Rocketdyne/AI administrators and union representatives reviewed our pay-code categorizations based on job title.

In summary, personnel records were used in this study to obtain information on personal identifiers for tracking vital status during follow-up (i.e., name, social security number, and birth date), pay codes and job titles for distinguishing salaried from hourly employees, and job titles and employment periods for developing proxy measures for selected chemical exposures (see below).

Data from Death Certificates

We received 334 death certificates of vested HPRMP members from the company. Company records also enabled us to determine vital status for workers currently employed—about 10% of the HPRMP cohort. We accepted this latter information only when two independent company data sources identified the employee as active at the end of follow-up.

Employees not identified as alive or dead with the help of company records were followed, using three different record systems designed to identify individuals who die in the United States. Specifically, we linked the Rocketdyne/AI personnel identifier data with information from (1) Social Security Administration (SSA) beneficiary-records files (cover period: 1935-94), (2) vital-statistics files for the State of California (cover period: 1960-94) and (3) the U.S. National Death Index (NDI) (cover period: 1979-94). All cohort members were matched against the SSA files and the vital-statistics files for the State of California. Due to the costs of the NDI service, we excluded from the NDI search all individuals known to be alive or dead on the basis of other sources, except for a verification sample covering 10% of all deceased employees. For all apparent record matches, we requested copies of the death certificates and determined whether the match was accurate after reviewing the information on those certificates.

From all sources combined, we have identified 875 deceased eligible HPRMP members who died between 1959 and 1994. We were able to obtain all but 30 (3.4%) of the death certificates from
Rocketdyne/AI or State Vital Statistics offices. We believe that at least 7 of those 30 death certificates are missing because the deaths occurred outside the United States. Thus, SSA files indicated that these 7 deaths occurred during the period covered by NDI, but NDI was unable to locate U.S. death certificates for these individuals. Where we have been able to retrieve non-U.S. death certificates, they have come from the Rocketdyne/AI beneficiary files.

We checked the reliability of the three computerized mortality-record systems used to ascertain the vital status of our cohort members. NDI correctly identified 97.8% (all but one) of the deaths from a 10% sample of known deaths. Other researchers have reported a sensitivity of 98% and 99.5% for the NDI search procedure (Rich-Edwards et al., 1994; Wiggs et al., 1994). The California vital-statistics-file records missed 5 (1.7%) of all California deaths identified by other means. About 21% of all deaths in our cohort occurred outside of California, but only 5 of these 175 out-of-state deaths occurred before 1979, and, therefore, could not be traced via the NDI system. Although the SSA search failed to identify 18.2% of deaths confirmed through other means, it identified correctly all non-California deaths that occurred before 1979, i.e., outside the period covered by the NDI system. Thus, the combined use of the three record systems was judged complete enough to justify the presumption that a person was alive at the end of follow-up if not identified as dead by at least one of the three computerized services or Rocketdyne/AI files.

A licensed nosologist coded the cause-of-death information recorded on each death certificate using the 9th revision of the International Classification of Diseases (ICD-9) (USDHHS, 1989; 1991). Both the underlying and associated (contributing) causes were coded, since associated causes can help to identify cancers with better prognosis that do not, by themselves, cause the individual's death. Nevertheless, associated causes of deaths will be included only in some "internal-comparison" analyses, since data available for the reference populations in the "external comparisons" are limited to rates for underlying causes. The coding was checked for accuracy, and discrepancies were discussed and reconciled by two members of the study team.
External Radiation: Sources of Data and Dosimetry

The major forms of external-radiation exposure (i.e., radiation produced outside the body) monitored at Rocketdyne/AI were gamma and X rays, but the records also contain readings for exposure to beta radiation and neutrons. All radiation records include whole-body dose measurements (i.e., estimates of the doses received by the tissues of the whole body). In this report, cumulative dose (i.e., the sum of all doses received from first monitoring to a given time) includes penetrating or deep exposures, but it excludes superficial skin doses and doses to the hands or feet alone. Neutron exposures were excluded from the study since they contributed only a small fraction of the total dose in the population and their inclusion raises considerable uncertainty about the appropriate quality factor (see Table 2.7). Records cover not only doses received by workers at the SSFL and Los Angeles area facilities, but also doses recorded during temporary assignments to non-Rocketdyne sites. All these exposures were included in our dose estimates.

If previous employment at nuclear facilities other than Rocketdyne/AI had been reported for an employee, Rocketdyne/AI records usually contained information about the radiation dose received at those facilities. Although this documentation of pre-employment radiation doses made it possible for us to add these to doses received at the study facility, most analyses in this report were restricted to doses received at Rocketdyne/AI. The major reason for this decision is that dose estimates from non-Rocketdyne/AI sources must be considered less reliable than measurements taken at Rocketdyne/AI, since it is unknown how consistently and accurately previous exposures had been documented and reported to Rocketdyne/AI. Tables 2.8 and 2.9 show the average doses previously received by HPRMP members and the number of workers for whom we found previous exposure records, by radiation dose received at Rocketdyne/AI. The availability of previous exposure records is two to three times greater for HPRMP members who received more than 10 mSv external radiation at the Rocketdyne/AI facilities than for those who received less than 10 mSv.
In addition, pre-Rocketdyne/AI exposures were usually reported as one cumulative dose instead of quarterly or annual doses. The Rocketdyne/AI records occasionally note that a previous employee had subsequently been employed at another nuclear facility, but no dose measurements are available.

The data from each individual's radiation files were organized by year and by radiation source (external or internal), then checked for validity and accuracy before being entered into our computer files by study personnel. Specifically, checks were performed to ensure that: (1) measurement dates were within the time of employment; (2) units of measurement were assigned and understood; (3) there were no duplicate records (the same record on the same date recorded several times in a file); and (4) where possible, cumulative doses reported for each year were equal to the sum of weekly, monthly or quarterly doses also reported for that year. Unclear information was discussed with two Rocketdyne/AI health physicists who have worked at Santa Susana since the 1950s and who are most knowledgeable about the radiation measurement and documentation procedures employed over time.

Files included film-badge, thermoluminescent-dosimeter, and pocket-chamber dosimeter readings. During some periods, readings were taken by more than one device—usually a film badge and a pocket dosimeter, and these multiple readings were identified as duplicate measurements. Whenever a film-badge reading was available, it was abstracted instead of the pocket-dosimeter readings for a given period. This choice is justified by the greater accuracy and reliability of film-badge measurement over pocket-dosimeter readings.

In the early 1950s, readings were taken on a monthly and sometimes a weekly or daily basis, driven by concerns about possible accidental short-term high-level exposures. In the 1960s, the company's monitoring policy changed, and quarterly readings from film badges became customary. Since film badges have a minimum detection limit (MDL) for recording dose equivalent, the more frequently readings are taken, the less likely the MDL will be reached for a given low dose. Thus,
the film-badge readings during the 1950s might underestimate the actual dose equivalent received by an employee. The threshold reported for the Landauer film badges used by Rocketdyne/AI throughout the follow-up period is 0.1 mSv.

Results of the A-bomb-survivor studies indicated increased cancer risks for dose equivalents above 200 mSv. Levels of 10 and 20 mSv have been used in several previous occupational-radiation studies as cut-points to define dose categories for statistical analysis. Thus, we decided to categorize dose equivalent for external penetrating radiation into 4 ordered groups: <10 mSv, 10 to <20 mSv, 20 to <200 mSv, and ≥200 mSv. We also treated cumulative dose equivalent (in mSv) as a continuous variable and explored the use of logarithmic transformations of dose equivalent (i.e., log(dose+1)).

Internal Radiation: Sources of Data and Dosimetry

Periodic bio-assays of urine or feces (measurements of radionuclide concentration in excreta) and in vivo whole-body or lung counts (measurements of the amount of radioactivity in the whole body and the lung) were obtained as measures of internal dose for workers assigned to areas potentially contaminated by radioactive materials. The doses resulted primarily from the inhalation and, to a lesser degree, ingestion of radionuclides produced or used in a wide variety of operations from 1952, at the start-up of the first nuclear reactor, to 1993, the last date for which internal dosimetry records were located in this study. The fuel-fabrication operations that were primarily responsible for internal doses involved almost exclusively uranium of different enrichment levels. We estimate that only about 50-60 individuals worked with materials containing plutonium at Rocketdyne/AI.

Most of the available internal-dose records were for the years 1963 to 1983, and the number of records prior to 1963 was low. A total of 2,617 unique files were examined, leading to slightly in excess of 100,000 separate measurements of internal radiation exposures. Of the 2,617 files, 2,294
(87.7%) belonged to HPRMP members.

The data abstraction has been supervised and the internal-dose construction performed by Dr. Douglas Crawford-Brown, a health physicist from the University of North Carolina at Chapel Hill. The following description of the internal-dose-estimation process relies heavily on his input.

The primary radionuclides analyzed were: (1) uranium, with a range of degrees of enrichment for U-235; (2) mixed fission products (unspecified as to radionuclide); (3) Sr-90; (4) Cs-137; and (5) plutonium. In addition, measurements of gross beta- and gross alpha-radiation in samples were performed on some individuals. A much smaller number of measurements were made of specific materials such as Hg and Po, but these did not contribute significantly to the population dose at the facilities. More than 90% of the internal-exposure records were urinalysis measurements for either uranium or for mixed-fission products.

For urinalysis measurements of uranium, the techniques employed were radiometric and fluorometric. The radiometric method is the more reliable for dose reconstruction, and so was used as the primary basis of dose estimation for uranium intakes in this study. In all instances where the radiometric method was used, the reporting units were disintegrations per minute (dpm) excreted per unit volume of urine. The fluorometric results (reported in units of micrograms, µgm) were used only as a check against the radiometric results, i.e., to ensure that both results yielded similar order-of-magnitude estimates of dose.

In addition, there were limited in vivo lung-counting results for U-235, indicated in the records as "IVLC" and reported in units of mgm. In most records, the raw measures had been converted to an estimate of the percent of the maximum permissible lung burden (%MPLB).

For the measurement of mixed fission products, radiometric urinalyses were performed by the facility and reported in units of disintegrations per minute (dpm) excreted per unit volume of urine. In only a few cases was it possible to determine the radionuclide present in the sample on the basis of information provided in the available records.
For the measurement of plutonium, radiometric analyses were also performed and reported either as dpm/volume or dpm/day (confirmed to mean dpm excreted per day).

For every individual, records were examined for each of the above radionuclides separately and sorted by calendar time within each year. A time-weighted-average measurement for an individual was then obtained for each year by weighting each reading in that year by the fraction of the year until the next reading in the temporal sequence. For example, if \( X_1 \) were a reading obtained on January 1 of a year and if \( X_2 \) were a reading obtained on July 1 of that same year, then the average for the year would be \( 0.5X_1 + 0.5X_2 \), since each reading would represent the exposure measure for approximately 50% of that year. The exception was at the end of the period of monitoring (indicated by the end of monitoring records for an individual), in which case the radionuclide was assumed to be removed with a half-life depending on the particular radionuclide (see the discussion below), and the resulting integral of activity versus time was calculated.

Methods for converting bioassay results to annual dose (in units of rads) were based on the biokinetic models of ICRP Publications 30 (1978) and 54 (1987) and on the mathematical techniques described fully in a report by Crawford-Brown et al. (1989). This approach yielded the following conversion factors for the primary radionuclides of interest:

1. For uranium urinalyses, each 15 dpm excreted per day is equivalent to an average dose of 0.5 rad to the lung tissue. This conversion factor is based on a mean removal half-time of uranium from the lung of 120 days and on the assumption that 80% of excreted uranium is through the urine. The dose to the bone marrow depends on the time since the onset of exposure. An average value of 0.05 rad per year to the bone marrow per 15 dpm/day urinary excretion has been assumed in this study, based on equilibrium conditions.

2. For uranium \textit{in vivo} lung counts, the conversion factor is obtained directly from the Rocketdyne/AI estimate of the percent maximum permissible lung burden. In each case, the time-averaged \%MPLB for an individual is multiplied by 0.15 rad. The conversion factor for the dose to
the bone marrow is approximately 0.02 rad per %MPLB.

(3) For mixed-fission products, the conversion depends on the availability of information on the radionuclide involved. In cases where the radionuclide was specified in the records (e.g., Sr-90 or Cs-137), committed effective dose equivalents had already been calculated by the facility health-physics staff. These calculations were confirmed and used as the dose for an individual. Where the radionuclide was not specified, a representative conversion factor based on an assumption of Sr-90 intakes and a Class Y retention half-time in the lung is employed. The resulting conversion factor is 0.5 rad per year to the lung per 250 dpm excreted per day.

(4) For plutonium, the conversion factor used was 1 rad/year dose to the lung per dpm/day. This factor is appropriate for a Class Y plutonium compound.

No policy that required uniform monitoring for all workers existed at Rocketdyne/AI. Rather, the health-physics team selected workers they judged to be potentially exposed to significant internal-radiation doses from airborne contaminants and included the selected individuals in a routine quarterly monitoring program; while other workers were monitored only in the event of accidents involving radioactive-material spills. Thus, there might be no measurements available for an individual during a certain period, even though exposure may have occurred. In most records, there is no indication of whether a bioassay reading was routine or the result of an accident. If the assay was the result of an accident, it is reasonable to assume that the intake occurred soon before the measurement. If no information was provided about the reason for the measurement, we assumed that the record represented a routine measurement. Consequently, the assumption of time weighting used in this study will overestimate doses for instances in which the measurement was due to an accident, but was not designated as such. Fortunately, it was possible to separate routine and accident-related measurements for individuals with large annual doses (in excess of 1 rad in a year). For other measurements, if the measurement was due to an accident, it is likely that the calculation of dose used in this study is an overestimate. This is
because it was assumed that the measurement reflected the average amount of radioactivity in the
body throughout the interval between that measurement and the next.

On the other hand, a potential for underestimation of the true average annual dose existed
due to the minimum detection limits (MDLs) of the assay methods in use (see previous subsection).
For uranium, the MDL corresponded to an annual dose of 0.2 rad; thus, our annual-dose averages
could be underestimated by as much as 0.2 rad if a burden slightly below the detection limit were
maintained throughout the year. For mixed-fission products, the problem was less acute, since the
MDL corresponded to an annual dose of 0.05 rad. For plutonium, the detection limit was
approximately 0.2 rad. In many cases, it was possible to avoid this problem by obtaining the
original measurement results and using the measured value rather than the administrative value;
but this option was not always available.

There were few internal-exposure records prior to 1963, despite the likelihood that internal
exposures may have been significant during that early period. The reason for the paucity of early
records is the practice adopted during that period of monitoring only those individuals with a
significant possibility of receiving annual lung-dose equivalents in excess of 150 mSv. After 1963, a
larger proportion of individuals were monitored routinely for purposes of reporting. It is
reasonable to conclude that the lifetime internal-dose estimates for individuals first employed
between 1953 and 1963 are often underestimates, although the degree of underestimation cannot be
determined.

For each year, employees could be assigned to one of four categories of internal dose. First,
there were individuals for whom no monitoring results were obtained. Second, there were
individuals for whom measurements were obtained, but all were less than the MDL. The doses for
this second class of individuals were higher than for those who fell into the first category, since a
determination had been made that the monitored individuals were working at locations with a
potential for exposure, and the MDLs for some of the radionuclides were high. Third, there were
individuals with positive readings in a year but with an estimated annual dose of 0.5 rad or less.

Finally, there were individuals with positive readings indicating an annual dose greater than 0.5 rad. The dose estimates for this fourth group of individuals will be the most reliable, since they were usually based on a clear separation of routine and accident-driven measurements.

Taking into account the above arguments about the validity and reliability of annual dose estimates for internal radionuclide exposures, we created two types of internal-radiation variables for purposes of analysis: (1) a binary variable indicating whether each worker was "monitored" or "not monitored" during a given period; and (2) cumulative dose equivalent for each worker (i.e., the sum of the annual dose equivalents from first monitoring to a given time, with a specified lag between cumulative dose measurement and outcome event), which was categorized into 4 groups: 0 mSv, >0 to 5 mSv, >5 to <30 mSv, and ≥30 mSv.

Chemical Exposures: Sources of Data and Measurement

Contrary to our expectations before starting data collection, Rocketdyne/AI did not provide us with air-monitoring data for carcinogenic chemicals between 1950 and 1984. We determined that exposure to hydrazine, asbestos, beryllium, and many solvents occurred at the facilities during this period, and we had originally planned to construct a job-exposure matrix for these chemicals. With the help of walk-through visits, interviews of managers and workers, and historical facility reports, we conducted an extensive industrial-hygiene review of the SSFL facility. For example, we were able to locate chemical inventories for the years 1955-94 for several chemicals of interest (e.g., hydrazine and solvents). We were also able to determine that most machinists could have been exposed to nitrosamines from cutting oils before the transition was made to water-based coolants in the early 1980s. The data collected during our industrial-hygiene review helped us to identify jobs, time periods, and work locations with a high probability of substantial exposure to certain chemicals such as hydrazine and asbestos.
We had planned to develop a job-exposure matrix based on the three major components: work location, job title, and period. As noted in previous interim reports, however, it soon became obvious that our ability to link workers with job locations was extremely hampered, since location codes on personnel cardexes do not actually identify the work locations of most employees. In general, we could only crudely link individual workers with one of the major Rocketdyne/AI facilities, but usually not with a room or even a building in which certain chemicals of interest were known to be used.

Nevertheless, we have been able to identify two location codes from personnel cardexes that are associated with asbestos exposure for mechanics (nuclear and liquid metal), engineers, and machinists who worked during certain periods in Area IV of the SSFL. Asbestos exposure was found to occur primarily in building 006 (sodium laboratory) and building 143 (sodium reactor experiment) of the SSFL before 1980. Thus, employees working between 1950 and 1980 in these buildings were exposed to airborne asbestos. Tasks particularly associated with high exposures involved cutting through and patching up asbestos insulation. Workers mixed bags of dry asbestos with water in a 5-gallon bucket until the mixture became mud-like. Interviews also revealed that workers did not wear respirators while performing such tasks before the early 1980s.

We created a 4-category variable to reflect a worker's expected or likely exposure to asbestos. The 4 exposure categories were defined as follows: "high" if the subject worked for more than 6 months before 1980 in building 006 or 143 and if his/her job title was any type of mechanic, machinist, or technician; "low" if s/he worked for more than 6 months before 1980 in building 006 or 143 and if his/her job title was any type of engineer; "potential" if (a) s/he worked for more than 6 months before 1980 in building 006 or 143 with another job title, or (b) his/her job title before 1980 was any type of mechanic, machinist, or technician and there was no mention in the personnel records of assignment to building 006 or 143; and "unexposed" otherwise. For purposes of analysis, asbestos exposure was treated as three binary variables (indicating the three "exposed"
categories). In addition, the 4 categories were collapsed into two--high vs. other--because we thought there might be considerable misclassification among the "other" categories and because we wanted to model the effect of each chemical exposure with only one variable (degree of freedom) to enhance precision. Table 2.10 shows the number and proportion of workers in the high asbestos group, by level of cumulative external-radiation dose.

An approach similar to the one described above for asbestos exposure was used to measure exposure to monomethyl hydrazine in personnel working at rocket-engine test stands in Areas I-III of the SSFL. For members of the HPRMP to have been potentially exposed to hydrazine, they would have to have been transferred from AI (Area IV) to the Rocketdyne division (Areas I-III) or vice versa. Workers were again grouped into 4 categories of expected or likely hydrazine exposure on the basis of job titles and employment periods, using information derived from worker and manager interviews and company-record reviews. The "high" exposure group includes workers employed for more than 6 months as propulsion/test mechanics or propulsion/test technicians. Some employees with these job titles have been responsible for loading hydrazine into test-stand fuel tanks and for loading Peacekeeper fuel tanks with hydrazine. These loading procedures officially involved "closed systems" to avoid exposure, but leakage of fuel from the systems was allegedly a common occurrence. The "low" exposure group includes workers with job titles who are very likely to have been present during engine firings involving hydrazine use, but who have not necessarily had direct contact with hydrazine. These job titles are propulsion/test inspector, test engineer, research engineer, and instrumentation mechanic. The "potential" exposure category includes workers with job titles who may have been present at engine test firings (e.g., flight-line mechanics and engineers), but for whom we have no way of confirming such possible exposure. The "unexposed" group includes all other workers. As with asbestos, the 4 hydrazine-exposure categories were also collapsed into two, high vs. other, for purposes of analysis. Table 2.11 shows the number and proportion of workers in the high hydrazine group, by level of cumulative
external-radiation dose.

Misclassification of hydrazine exposure using our approach is probably greater than misclassification of asbestos exposure. Not only is it impossible to determine from job titles which workers were actually assigned to rocket-test stands or buildings in Areas I-III where hydrazine was used, but also exposure to hydrazine was more likely to result from accidental and unpredictable occurrences.

General Analytic Approach

In this section, we describe two different analytical approaches used in this study: (1) external comparisons of our monitored workers with two national reference populations; and (2) internal comparisons of monitored workers according to measured dose levels of radiation exposure (dose-response analyses).

The relative advantage of external comparisons is that large reference populations, such as the general U.S. population, provide more power and precision when rare outcome events are examined (e.g., death from leukemia or brain cancer). On the other hand, such external comparisons are limited for estimating radiation effects because there are likely to be many differences between Rocketdyne/AI workers and the comparison population, aside from radiation exposure, that can affect morbidity and mortality. We seldom have adequate data on other risk factors in the external population to control analytically for bias caused by these differences. Typically, workers selected for many jobs tend to be healthier, on average, than members of the general population, so that we expect lower mortality rates in worker populations. This phenomenon, called the "healthy-worker effect," makes the interpretation of external comparisons problematic.

Consequently, we rely primarily on the internal comparisons to estimate radiation effects in this study. External comparisons are used to describe the study population, to assess the net
influence of healthy-worker effects that are operating in this worker population, and to identify specific cancer sites with elevated mortality rates that might be explained by the effects of radiation (or other occupational exposures) estimated from the internal comparisons. To enhance the interpretation of external comparisons, we have performed these analyses separately for two different reference populations: the general U.S. population, and a compilation of worker populations assembled by the CORPS project of NIOSH from other occupational studies (Zahm, 1992; see Table 4.1.a for a list of studies included in this reference population). These two reference populations allow us to make complementary contrasts with different selection processes at work. While the general U.S. population includes many individuals with cancer and in poor health, the NIOSH cohorts include relatively healthy workers who were selected in part because of exposures to toxic chemicals that were thought or hypothesized to be carcinogenic.

Statistical Methods: External Comparisons

We used the Monson (1994) program to estimate expected numbers of deaths and standardized mortality ratios (SMRs) for the Rocketdyne/AI population or subpopulation. Expected numbers of deaths were based on mortality rates observed in the two reference populations described above, stratifying on age (5-year strata), sex, and calendar year (5-year strata). Each SMR represents the estimated mortality rate for the Rocketdyne/AI cohort divided by the corresponding mortality rate for the reference population (i.e., the rate ratio), standardized to the age-sex-year distribution of the Rocketdyne/AI cohort. We present the mortality results for all causes of death, all cancers, specific types of cancer (including the groupings used in the internal comparisons—see below), and other major diagnostic categories such as cardiovascular, respiratory, genito-urinary, gastrointestinal, and external causes (Monson, 1994).

The reference database compiled by the NIOSH-CORPS program pools mortality data from 39 occupations and industries (see Table 4.1.a). Use of mortality rates derived from this
pooled dataset is supposed to help minimize comparison problems caused by "healthy-worker effects" (see below), incomplete ascertainment of deaths, and other complications encountered in occupational cohort studies. Another helpful feature of the NIOSH-CORPS project is that it provides separate rates for salaried and hourly employees. On the other hand, the limited number of cancer deaths in the NIOSH population prevented us from estimating SMRs for specific types of cancers, as was done with the U.S. population.

The ICD-9 codes provided by our nosologist for deceased cohort members were first translated by the Monson program (1994) from ICD-9 codes to the codes in use at the time of each death, then translated again to the ICDA-8 codes used for the SMRs reported in Tables 3.1-3.6. Estimation of variances and 95% confidence limits for the SMRs involving the U.S. population was based on the method of Byar, which was recommended by Breslow and Day (1987). These variances and confidence limits are estimated under the assumption that the stratum-specific rates for the U.S. reference population are fixed (with zero variance). Since this assumption would not hold for the NIOSH reference population, we had to use another method. In the absence of available software for exact estimation with stratified person-time data, we used the asymptotic method of Greenland (1982) in which all strata with no outcome events (deaths) were excluded and 0.5 was added to each cell of every stratum with one zero cell. Since the information on death certificates indicated that 96% of all Rocketdyne/AI employees were white, we applied only the rates for white members of the external reference populations to the HPRMP cohort (see also the section on Confounding... for a discussion of race information).

Since the externally monitored and internally monitored cohorts involved different groups of workers in the HPRMP, we performed separate external comparisons for these two groups. As noted previously, all but 44 of the internally monitored group are included in the externally monitored group. Analyses stratified by pay type (salaried vs. hourly) included only those HPRMP-cohort members for whom pay type was known (see Tables 2.2 and 2.5).
Statistical Methods: Internal Comparisons

In comparing the mortality patterns associated with different levels of exposure within each monitored group, it was not possible to treat each cancer site as a separate outcome variable because there were not enough deaths for most cancer types to yield informative dose-response analyses. Thus, the outcomes examined in the internal comparisons are restricted to deaths from all cancers combined and from specific groups of cancers that were classified as radiation-sensitive (radiosensitive) in BEIR V (1990). For the dose-response analyses of external radiation, we created two a priori groups of radiosensitive cancers: (1) all hemato- and lymphopoietic cancers (ICD-9 200-208), excluding chronic lymphocytic leukemia; and (2) all solid cancers identified as radiosensitive in BEIR V, including lung cancer (see below). In addition, analyses were conducted separately for the most common type of cancer death in our study population—lung cancer (ICD-9 162).

In addition to lung cancer, the solid-radiosensitive-cancer group includes cancers of the esophagus (ICD-9 150), stomach (ICD-9 151), colon (ICD-9 153), brain (ICD-9 191-192), breast (ICD-9 174), and urinary-tract system (ICD-9 188-189). Bone and thyroid cancers are not included because no deaths from these causes were identified in our study population. Thyroid cancers have been primarily linked to childhood radiation exposure, and there is little evidence that they are affected by exposure to radiation during the adult years (Boice, 1996). It should be noted, however, that breast and thyroid cancers might be underrepresented in our mortality data because they are relatively nonfatal. Although we excluded the 4 chronic-lymphocytic-leukemia (CLL) deaths from the analyses of hemato- and lymphopoietic cancers presented in this report (since they are generally not considered to be radiosensitive), we also performed some of these analyses by including these 4 CLL deaths as outcome events; the estimated radiation effects did not change appreciably.

For the dose-response analysis of workers monitored for internal-radiation exposure, it is
important to recognize that the internally deposited radionuclides of major concern in this study emit densely ionizing alpha-radiation that usually reaches and damages only the tissues in its immediate vicinity, within micrometers of the particle (ICRP, 1980). However, the air-filled spaces in the lung allow alpha particles to reach greater distances, such that almost any tissue constituent of the lung may receive a considerable dose of radiation. Larger particles rarely reach the lower respiratory tract or, if they do, are cleared rapidly and completely. On the other hand, such particles can deliver large doses of alpha radiation to minute regions of the naso- and oropharyngeal systems and the gastrointestinal tract, even if their residence time is no longer than a few days. Furthermore, relatively insoluble radioactive particles that reach the alveolae are gradually translocated to tracheobronchial and other thoracic lymph nodes, which may accumulate concentrations of inhaled material several hundred times greater than in the regions of the lung (ICRP, 1980).

Given the above properties of internally deposited radionuclides, we examined their effects on the organ systems through which radioactive particles pass from intake to excretion. For dose-response analyses of internal radiation, we grouped together "upper-aerodigestive-tract cancers" of the naso-oropharyngeal regions, esophagus, and stomach (ICD-9 140-151). A similar grouping has been used in other epidemiologic studies of these rare cancers (e.g., Benner et al., 1995; Spitz, 1994). In separate analyses, we also examined radionuclide effects on hemato- and lymphopoietic cancers (ICD-9 200-208), lung cancer (ICD-9 162), and urinary-tract cancers (bladder and kidneys; ICD-9 188-189). Other organs to which radioactive materials are translocated and in which they are sometimes concentrated--depending on their solubility, chemical structure, affinity to certain tissues, etc.--are the liver and bones. We did not, however, observe any deaths from bone or primary liver cancers among HPRMP members monitored for internal radiation.

For the internal comparisons of monitored workers according to cumulative radiation dose, we used the risk-set approach of Breslow and Day (1987) for cohort studies. In this approach,
conditional logistic regression is used to compare individuals who have died of cancer with individuals still at risk of dying from cancer ("survivors")--a method that resembles the analysis of matched case-control data. We constructed risk sets of deaths and survivors for use in the analysis by matching to each cancer death, d, who died at time t, all m cohort members who were still alive at time t. Thus, we did not sample a fraction of survivors (controls) for each death from the complete risk set (case-cohort sampling), a procedure that reduces the number of survivors in the analysis and has been employed in other studies to minimize the amount of required computer memory. Consequently, an individual contributed to multiple risk sets from his/her time of entry into the cohort (start of monitoring or 1/1/50) until the end of follow-up (12/31/94) or his/her death. The principle of weighting each individual according to length of follow-up in person-time is retained in this approach, since the longer an employee belongs to the cohort, the more often s/he will be eligible as a comparison subject. This procedure provided us with an average of 3,578 survivors for each cancer death.

Rate ratios (RR) and 95% confidence intervals (CI), comparing each exposed group with the reference group, were derived from the estimated model coefficients and their standard errors. These estimated coefficients (\ln\{rate ratios\}) obtained from conditional logistic analysis of risk sets are comparable to those obtained from a proportional hazards model (e.g., Gilbert et al., 1989) or a finely stratified Poisson model (e.g., Wing et al., 1991). By including other covariates (predictors) in the model, we controlled for the effects of confounding variables such as sex, calendar period, age at exposure, time since first exposure, and age at the time of the index case's death (called "age at risk"). This approach also allowed us to treat cumulative radiation dose and certain other variables (e.g., time since first monitored) as time dependent, meaning that the value for an individual can change over time during the follow-up period. Cumulative radiation dose was treated in separate analyses as a set of three binary variables (indicating the three nonreference dose categories) or as one continuous variable. To test for trend across dose categories using
logistic regression, the mean doses for all subjects in each category were used as exposure scores.

We explored the effect of "total cumulative lifetime dose" by adding to the dose received at Rocketdyne/AI any penetrating-radiation doses documented for previous employment at other facilities. As noted earlier, however, most analyses in this report were restricted to doses received at Rocketdyne/AI, because we believe that pre-Rocketdyne/AI doses were not completely documented in Rockwell records and the level of documentation may be associated with the radiation dose received at Rocketdyne/AI. The only reported findings involving the analysis of total cumulative lifetime dose are shown in Tables 3.7 and 3.9 (first column of estimated effects).

Cumulative radiation dose received at Rocketdyne/AI was treated as a time-dependent variable in all analyses. Time-dependent treatment of radiation dose involves updating the cumulative dose for each subject at risk at the time of each outcome event (cancer death). To allow for varying periods of induction/latency between radiation exposure and cancer death, cumulative doses were lagged by 0, 2, 5, 10, 15, and 20 years. Lagging was achieved by limiting the cumulative dose for each individual in a risk set to the dose received 0, 2, 5, 10, 15, or 20 years before the index death.

In using a logistic model to estimate effects, we assume that the logit of the probability of dying from the index cancers in an interval, conditional on being alive at the start of that interval, is a linear function of the covariates (Hosmer and Lemeshow, 1989). Thus, if the covariates are a linear function of untransformed variables, the effects of any two covariates are assumed to be multiplicative on the odds scale. According to Breslow and Day (1987:160), such multiplicative relative-rate models are preferred to additive relative-rate models used in several other studies (e.g., BEIR V, 1990) for estimating radiation effects, because the estimated parameters of the linear relative-rate model are unstable. This problem is particularly relevant to our analyses due to the small numbers of cancer deaths. Furthermore, the limited size of our dataset did not allow us to distinguish adequately among alternative model forms.
We modeled exposure both as a set of binary variables and as a continuous variable for cumulative dose in mSv. Log transformations of the continuous variable (log[dose+1]) were also explored. The log transformation of dose is equivalent to using a multiplicative power model, which approximates the additive risk model (Breslow and Day, 1987:159).

In all models, we explored the influence of confounding factors, such as the ones discussed below, but only the results of reduced models will be presented in this report. The covariates—pay type, time since first monitoring, and age at risk—were retained in all final models. For other potential confounders, we followed the change-in-effect criterion recommended by Greenland (1989) in order to determine whether a covariate should be removed from a model. Specifically, the covariate remained in the model if its inclusion changed the estimated rate ratio for radiation dose by more than 10%. Effect modification was evaluated by adding interaction (product) terms to the models and, for age and dose, by other methods described in the next section.

To estimate the number and fraction of cancer deaths attributable to occupational exposure to radiation, we used the logistic-regression results for each cancer outcome, where cumulative external or internal radiation dose is modeled as indicator variables for three nonreference categories (i = 1...3). The attributable fraction for the i-th dose category (AF$_i$) was approximated as (RR$_i$-1)/RR$_0$, where RR$_i$ is the estimated rate ratio, derived from the logistic-regression results with zero lag, for the i-th dose category (i > 0) compared with the reference category (i = 0) (Rothman, 1986:38-39). Thus, the estimated attributable fraction for the total population (AF)—i.e., the proportion of all cancer deaths (of one type) attributable to a radiation dose greater than the reference value—is approximately 1 minus the sum (across all dose categories, i = 0...3) of (A$_i$/A)/RR$_0$, where A$_i$ is the number of cancer deaths in the i-th dose category, A is the total number of cancer deaths (of one type) observed in the study, and RR$_0$ = 1. Therefore, the number of cancer deaths (of one type) that were attributable to the effect of radiation—i.e., the attributable number—is AF times A. By summing the estimated attributable numbers for all types of cancer found to be
positively associated with external or internal radiation dose, we estimate the total number of observed cancer deaths (of all types) attributable to radiation received at work during the follow-up period in the cohort of monitored workers.

Confounding, Effect Modification, and Misclassification Bias

When estimating the effect of external or internal radiation on cancer mortality, the cumulative dose for each type of radiation was treated as a potential confounder of the other effect. In analyses of the externally monitored group, internal dose for workers not internally monitored was set equal to zero.

We created several binary variables to explore the effect of age at risk on cancer mortality. There was no advantage to using binary variables versus a continuous variable in adjusting for the confounding effect of age; therefore, we treated age as continuous in all models. In certain models involving age stratification (described below), we adjusted for age at risk in another way--by post-matching survivors to cancer deaths on age (± 1 year) when creating the risk sets for analysis.

Since follow-up started at first monitoring, "time since first monitoring" in our analyses is analogous to the "time since hire" or "time since start of follow-up" in other occupational cohort studies. Recently, there have been discussions in the literature about the potential confounding effect of such time-related variables as time since hire in cohort studies using cumulative exposure measures (Flanders et al., 1993; Steenland and Stayner, 1991; Arrighi and Hertz-Picciotto; 1995). Flanders et al. (1993) argue that it is essential to control for this variable in order to remove the bias caused by the decline in health status after the start of employment, which is positively associated with cumulative exposure. Arrighi and Hertz-Picciotto (1995) showed that other variables capturing the time effect in cohort studies, such as calendar period and current age or age at hire, are highly correlated with time since hire. Thus, adjusting for time since hire in addition to the other time-related variables might have little influence on the effect estimates for cumulative
exposure.

When examining the effect of time since first monitoring in the analyses for either external or internal radiation exposure in our cohort, we found that some estimated rate ratios for radiation dose changed more than 10%. We therefore adjusted for time since first monitoring in all models used to estimate the effects of external and internal radiation. Time since first monitoring was treated as time dependent; i.e., its value changed for a survivor from risk set to risk set, depending on when the index death occurred.

According to the A-bomb survivor studies, age at exposure modifies the effect of radiation exposure. Thus, at comparable doses and ages at risk, cancer incidence was observed to be higher for persons who were exposed as children than for those who were exposed as adults (Thompson et al., 1994). A previous reanalysis of occupational cohort studies, however, suggested the opposite relationship between age at exposure and the effect of cumulative low-level radiation dose in the adult years (Kneale and Stewart, 1993; 1995; Stewart and Kneale, 1996). According to Kneale and Stewart, employees of nuclear facilities exposed at older ages (> 50-65) experienced higher cancer-mortality rates than did employees exposed at younger ages to comparable dose levels, conditional on age at risk and other factors.

We decided to examine the dependence of the external-radiation effect on age at exposure in several ways. First, we used age at first monitoring as a surrogate for age at first exposure in the analyses where we had time-matched survivors to deaths. We could not use "age at the mean of the monitoring period" or "age at peak exposure," because in any risk set, some survivors would not have reached their mean or peak exposure by the occurrence of the index death. Age at first monitoring was treated as a continuous covariate in the model and centered around its population mean. Second, we assessed interaction effects, using product terms in the model, between cumulative (time-dependent) radiation dose and two age variables: age at first monitoring and age at first exposure to more than 10 mSv. Third, we examined separately the effects of binary
variables indicating exposure after the age of 40, 45, 50, 55 and 60 years, controlling for cumulative dose. Fourth, we post-matched survivors to cancer deaths on time of death and age at risk (± 1 year); then, we created a separate cumulative dose variable for each of three age intervals ("windows"): < 40 years, 40-49 years, and > 49 years. Then all three age-specific dose variables were added to the model, along with other covariates. In this report, we present only the results of this fourth method because we believe the results are easiest to interpret.

Pay-type and job-title information from personnel records were used to generate a three-category proxy measure for socioeconomic status (SES); union employees paid on an hourly basis were distinguished from salaried technical/administrative employees and salaried managerial/professional employees. Since some employees changed pay type or job title, we categorized each worker according to the job title and pay type held longest at Rockwell. Due to missing personnel records, we were unable to identify pay type for 211 HPRMP members. In our preliminary attempts to model the effects of pay type on cancer mortality, we treated workers with unknown pay type as a separate binary variable, and we used mean imputation to deal with the missing values. Subsequent efforts, however, to reduce the number of covariates in the model suggested that it was sufficient to treat pay type as a binary variable—salaried professional/managerial vs. all other pay-type groups, including unknown—in order to adjust efficiently for the confounding effect of this variable.

Information about tobacco smoking was systematically recorded for a subgroup of HPRMP members. Medical questionnaires from certain periods provided us with information about smoking at first employment and at annual medical examinations. Questionnaires from 1961 to 1969 indicated only if the worker was a smoker (yes/no); from 1970-1980, no smoking information was provided; after 1980, the amounts and dates of smoking and quitting were specified. Since smoking information was available for only 1,096 HPRMP members, we were unable to control for the effect of smoking in the total cohort. Thus, to assess potential confounding by smoking, we
examined the associations between smoking and cumulative radiation dose and between smoking and pay type in the subsample of 1,096 subjects (see Tables 3.14-3.19).

Since Rocketdyne/AI did not systematically collect data on the race of its employees before 1972, we were unable to control for the influence of this variable in our analyses, since most subjects were hired before 1972. According to the information on death certificates, however, 96% of all deceased workers were white. Computerized personnel data for Rocketdyne/AI employees showed that the race/ethnicity distribution after 1971 was: 82% white/Caucasian, 6.5% Hispanic, 6% African American, 5.2% Asian, and 0.3% other groups. Thus, the HPRMP cohort can be characterized as overwhelmingly white. Tables 2.2-2.5 show that it was also overwhelmingly male. When gender was added as a covariate to our models, it did not change the effect estimate for radiation dose. Therefore, the results presented in this report are not adjusted for gender.

We also assessed the potentially confounding effects of chemical exposures by adding to models time-dependent binary covariates for asbestos and hydrazine exposures (see the previous section). Since the effect estimates for radiation dose did not change appreciably (i.e., by > 10%) when controlling for these covariates, the results presented in this report are not adjusted for asbestos or hydrazine.

3. RESULTS

External Comparisons

The results of comparing the mortality experience of Rocketdyne/AI workers monitored for external radiation with two other reference populations are shown in Tables 3.1 and 3.2. In Table 3.1, males in the externally monitored study population are compared with white males in the U.S. population. In Table 3.2, males in the externally monitored study population are compared with white males in the NIOSH reference population, stratified by pay type (salaried vs. hourly). The
mortality rates for all causes and for all cancers were markedly lower in externally monitored male workers than in U.S. white males (SMR = 0.68, 95% CI 0.64-0.73; and SMR = 0.79, 95% CI 0.69-0.89, respectively). Similar results were obtained for all causes of death when comparing monitored workers with the NIOSH reference population (SMR = 0.79 for salaried workers and 0.78 for hourly workers), but the mortality rates for all cancers were similar (SMR = 0.99 for salaried workers and 1.02 for hourly workers). Although none of the 95% confidence intervals for specific cancers in Tables 3.1 or 3.2 exclude the null value, there does appear to be some excess mortality from leukemias in the Rocketdyne/AI cohort; the SMR, using the U.S. population as the referent, is 1.60 (95% CI 0.95-2.52). From the comparisons with the NIOSH population, we see that the excess leukemia mortality is restricted to salaried employees (SMR = 2.05; 95% CI 0.83-5.04). Compared with the NIOSH population, both salaried and hourly Rocketdyne/AI workers experienced much lower mortality rates for arteriosclerotic heart disease (SMR = 0.68, 95% CI 0.45-1.04; and SMR = 0.75, 95% CI 0.59-0.95, respectively).

The mortality experience for female Rocketdyne/AI workers monitored for external radiation is shown in Table 3.3. Although the SMRs for all causes and all cancers are similar to the results for males, these analyses are not very informative because we observed only 31 deaths among female employees.

The results of comparing the mortality experience of male Rocketdyne/AI workers monitored for internal radiation with the two white male, reference populations are shown in Tables 3.4 and 3.5. These results are generally similar to the results for the larger externally monitored group (Tables 3.1 and 3.2), but with wider confidence intervals. The SMR, comparing Rocketdyne/AI workers with the U.S. population, is 0.72 (95% CI 0.66-0.80) for all causes and 0.87 (95% CI 0.73-1.03) for all cancers (Table 3.4). In comparisons with the NIOSH population (Table 3.5), we again see some excess leukemia mortality that is restricted to salaried workers (SMR = 1.81, 95% CI 0.66-4.98).
The mortality experience for female Rocketdyne/AI workers monitored for internal radiation is shown in Table 3.6. Again, the results are not very informative because we observed only 8 deaths among these employees.

Since we are not able to adjust for smoking in our external comparisons and since smoking is a risk factor for several cancers, it is informative to compare the frequency of cigarette smoking in Rocketdyne/AI employees with the frequency of smoking in the reference populations. In 1965, 51.3% of all U.S. white males greater than 20 years of age and 60.1% of white males between the ages of 25 and 34 were cigarette smokers (U.S. Surgeon General, 1979). Between 1961 and 1969, 63.4% of all Rocketdyne/AI employees (mean age 31 years) were smokers. In 1980, 37.1% of the U.S. white male population greater than 20 years of age were cigarette smokers (U.S. Surgeon General, 1983), and this proportion dropped to 28% in 1990. Among Rocketdyne/AI employees between 1982 and 1984, the proportion of smokers was 37.4% among hourly workers and 19.5% to 24.7% among salaried workers. Thus, since Rocketdyne/AI employees seem comparable to the general U.S. population of white male adults with respect to smoking behavior, the estimated SMRs were probably not confounded very much by smoking.

Internal Comparisons: External-Radiation Effects

Table 3.7 shows the distribution of total cumulative external-radiation doses for all externally monitored subjects, for those who died from any cause, and for those who died from any cancer. This table also shows how the exposure distribution for cancer deaths changes when radiation dose is lagged by various amounts ranging from 0 to 20 years, and it shows the exposure distribution for cancer deaths, with zero lag, when pre-Rocketdyne/AI doses are included.

The final logistic models for estimating the effects of external radiation among externally monitored workers include the following predictors: age at risk, time since first monitoring, pay type, cumulative dose of external radiation, and cumulative dose of internal radiation. Table 3.8.a
shows the adjusted rate-ratio (RR) estimates for each predictor, by type of cancer outcome, assuming a zero lag (excluding pre-Rocketdyne/AI doses). Table 3.8.b presents crude and adjusted rate-ratio estimates for the effects of external radiation dose, assuming a 15-year lag. Table 3.8.c shows the results of the zero-lag analysis redone to include as outcome events both underlying causes of death (as in previous tables) and associated (contributing) causes. This alternative approach does not change the estimated effects of external radiation.

The results in Tables 3.8.a-c show that cancer-mortality rates increase monotonically with external-radiation dose for total cancers (p for trend = 0.036, Table 3.8.a) and for all radiosensitive solid cancers (p = 0.12), but not for cancers classified as nonradiosensitive (p = 0.58). Although the trend for hemato- and lymphopoietic cancers was not perfectly monotonic across the 4 dose categories (p = 0.003), the rate was particularly elevated for the highest dose group (≥ 200 mSv), which contained two index deaths (RR = 15.7; 95% CI 3.33-73.5). A similar pattern was observed for lung cancer. Although the trend was not perfectly monotonic (p = 0.045), the rate was particularly elevated for the highest dose group, which contained two lung-cancer deaths (RR = 4.70; 95% CI 1.05-21.0).

Table 3.9 shows the estimated effects of external radiation dose measured as a continuous variable with different lags (0-20 years). The rate-ratio estimates for lung cancer decline with increasing lag greater than 2 years. In contrast, the rate-ratio estimates for hemato- and lymphopoietic cancers and for all cancers increase somewhat with increasing lag. The estimates for radiosensitive solid cancers do not change much with different lags. The widths of the confidence intervals around the rate-ratio estimates increase with increasing lag because of the decline in the number of observed deaths. Furthermore, the likelihood ratio chi-square statistic is fairly uniform across all lag periods. Thus, although it is difficult to identify a "best-fitting" model on the basis of likelihood ratio statistics, the largest values are observed for a 10-15-year lag with hemato- and lymphopoietic cancers and for a 0-5-year lag with lung cancer.
We observed no interaction effects (on the multiplicative scale) between cumulative dose and either age at first monitoring or age at first exposure to more than 10 mSv, controlling for these main effects and other covariates. When effects were estimated separately for cumulative doses received during three age internals, however, the results suggest that age at exposure might modify the effect of external radiation on cancer mortality (Tables 3.10.a-b). Although the power for testing these age-specific effects is low, the pattern of effect modification by exposure age appears to vary by type of cancer outcome. While the effects of radiation on total cancers, radiosensitive solid cancers, and lung cancer are largest for doses received after age 50, the effect on hemato- and lymphopoietic cancers is largest for doses received before age 50.

When adding our measures of asbestos and hydrazine exposures to the models, we observed little changes in the estimated radiation effects; thus, these chemical exposures do not appear to confound the effect of external radiation on cancer mortality. The associations between smoking status measured at different periods and cumulative external-radiation dose among samples of workers are shown in Tables 3.14, 3.16, and 3.18. Since smoking is not systematically associated with radiation dose in any period, it appears that smoking probably was not an important confounder of the external-radiation effects estimated in our dose-response analyses. On the other hand, smoking is associated with pay type (see Tables 3.15, 3.17, and 3.19), suggesting that pay type might have served as a proxy for smoking in our analyses.

Since external radiation was associated with both hemato-lymphopoietic cancers and radiosensitive solid cancers, we estimated the numbers of deaths from these cancers attributable to external radiation at Rocketdyne/AI. As described in the Methods section, these estimates take into consideration radiation effects estimated from the logistic-regression analyses as well as the distribution of external-radiation doses received by monitored workers at Rocketdyne/AI. We found that about 5 deaths from hemato-lymphopoietic cancers and about 4 deaths from radiosensitive solid cancers (including lung cancer) during the follow-up period were attributable to
cumulative external doses greater than or equal to 10 mSv. These 9 deaths represent 3.5% of all cancer deaths observed in the externally monitored cohort and 11.1% of "exposed" cancer deaths with cumulative doses of 10 mSv or more.

Internal Comparisons: Internal-Radiation Effects

Table 3.11 shows the distribution of cumulative internal alpha-radiation dose for all internally monitored workers, those who died of any cause, and those who died of any cancer. This table also shows how the exposure distribution of cancer deaths changes when radiation dose is lagged by 0-20 years. The number of highly exposed cancer deaths decreases only slightly with increasing lag, indicating that most radiation exposure occurred more than a decade before the cancer deaths.

Table 3.12.a shows the estimated effects of internally deposited radionuclides on the organ systems discussed in the Methods section, with zero lag, controlling for external radiation dose, pay type, age at risk, and time since first monitoring (for internal radiation). A strong monotonic association is observed between cumulative internal dose and mortality from cancers of the upper-aerodigestive tract (p for trend = 0.0001), even though no effect of external radiation was observed for these cancers. A strong monotonic trend was also observed for hemato- and lymphopoietic cancers (p = 0.0001). Unlike the results with external radiation, these dose-response associations are not entirely dependent on small numbers of deaths in the highest dose category (≥ 30 mSv). We found no effects of internal radiation on mortality from urinary-tract cancers (kidney and bladder; see Table 3.12.a). Although there was an inverse association observed between internal-radiation dose and lung-cancer mortality, this result was probably a chance finding (p for trend = 0.20).

Because of its effects on hemato-lymphopoietic and upper-aerodigestive-tract cancers, cumulative internal dose is also associated with total-cancer mortality (p for trend = 0.087). Lagging doses by 15 years or including cancers listed as associated causes on death certificates does
not change these results (see Tables 3.12.b-c). Furthermore, the estimated effects of internal radiation do not change appreciably when adding our measures of asbestos and hydrazine exposures to the models.

We estimated that about 6 deaths from hemato-lymphopoietic cancers and about 9 deaths from upper-aerodigestive-tract cancers during the follow-up period were attributable to cumulative internal doses greater than 0 mSv. These 15 deaths represent 11.2% of all cancer deaths observed in the internally monitored cohort and 27.3% of "exposed" cancer deaths with cumulative doses greater than 0 mSv.

The combined effects on total-cancer mortality of both external and internal radiation, cross-classified into 9 dose categories, were estimated for all 2,253 workers monitored for both external and internal radiation. The results of these analyses are shown in Table 3.13.a (with zero lag) and Table 3.13.b (with a 15-year lag). Although there are no cancer deaths in the highest combined dose category ($\geq 200$ mSv external and $\geq 30$ mSv internal), the cancer-mortality rate is elevated appreciably (i.e., RR $> 5$) for monitored workers in the highest dose category of one radiation type and in the next highest category of the other type (20-199 mSv external or 6-29 mSv internal). Nevertheless, the 95% confidence intervals for these estimates are quite wide.

4. DISCUSSION

External Comparisons

Total mortality and total-cancer mortality were lower in our radiation-monitored cohorts than in the general U.S. population. When we stratified the monitored cohorts by pay type (salaried vs. hourly) and compared them with similar strata in the male NIOSH population, however, mortality from all cancers was similar for externally and internally monitored workers. Furthermore, male salaried Rocketdyne/AI employees monitored for external or internal radiation
experienced elevated mortality rates from leukemias.

The all-cause SMR (0.68; 95% CI 0.64-0.73), comparing Rocketdyne/AI workers with the U.S. population, illustrates the well-known healthy-worker effect. That is, most employed populations have consistently been shown to have lower death rates from all causes than does the general population. This does not mean that being employed decreases the risk of dying, but rather that healthier individuals are more likely to get employed and stay employed than are less healthy individuals. A review article by Park et al. (1991) pointed out that the mean SMR for employees from nuclear industries is even lower than the mean SMR for all industries combined (SMR = 0.79 vs. 0.83). Our review of the literature corroborated this finding. Within the nuclear industry, SMRs for all employees (including both those monitored and those not monitored for radiation) are slightly higher than the SMRs reported for monitored employees alone (Table 1.2.a). Our all-cause SMR of 0.68 for externally monitored Rocketdyne/AI workers is lower than the mean SMR reported by Park et al., and it is lower than most of the SMRs listed in Table 1.2.a. The selective hiring and retention of healthy workers, therefore, may be more pronounced at Rocketdyne/AI than in most other studied occupational cohorts.

We believe that one reason for the strong healthy-worker effect in some of the nuclear-industry facilities is the high percentage of highly educated employees in research facilities such as Rocketdyne/AI. About 45% of our cohort members were salaried professional, technical, or managerial employees, many of them scientists. The total-mortality SMR of 0.68 for our cohort is comparable to the SMR of 0.63 (95% CI 0.60-0.65) reported for employees of the Los Alamos National Laboratory (Wiggs et al., 1994), another nuclear facility with a strong emphasis on research. Park et al. (1991) describe a strong impact of socioeconomic status on SMRs in occupational cohorts. According to these authors, U.S. cohorts consisting of professionals (e.g., managers, engineers, architects, pathologists, and chemists) have all-cause SMRs ranging from 0.5 to 0.7; and British studies have shown a linear decrease in all-cause and total-cancer SMRs with an
increase in social class (from unskilled to professional) for men of working age. It is not surprising, therefore, that the low all-cause SMR persisted when we compared the Rocketdyne/AI employees to the total NIOSH population, since about 90% of the NIOSH population was hourly workers. We would expect more valid comparisons by stratifying on pay type, since this stratification should help to control for differences between Rocketdyne/AI and the total NIOSH cohort in the distribution of socioeconomic status and related factors.

When salaried and hourly workers from the externally monitored group were compared with the corresponding NIOSH groups, the resulting all-cause SMRs remained low: 0.78 and 0.77, respectively. These low SMRs are due primarily to the relatively low mortality rate from circulatory diseases in our cohort, especially arteriosclerotic heart disease (SMR = 0.68 and 0.75, respectively). A low SMR (0.57; 95% CI 0.54-0.60) for circulatory diseases was previously described for Los Alamos employees, indicating a similar selection effect for employees at that nuclear facility.

For both externally and internally monitored cohorts, the observed total-cancer mortality rates among Rocketdyne/AI salaried and hourly employees were similar to the corresponding rates in the NIOSH population. Nevertheless, elevated mortality rates for leukemias were consistently observed in Rocketdyne/AI groups, especially for salaried workers. These latter results may be due in part to the effects of occupational radiation exposure that we found in the internal comparisons. In addition, we found excess mortality rates for other specific cancers in the external comparisons, but these elevated SMRs were not observed consistently across different analyses and they are based on small numbers of deaths.

One limitation of the external comparisons stratified on pay type is that this variable does not entirely characterize individual workers in the NIOSH reference population, but only each study cohort as a whole. That is, NIOSH epidemiologists and industrial hygienists classified each study cohort as "ever blue collar" (hourly workers) on the basis of general characteristics of that
cohort. Thus, the population of "hourly" NIOSH workers actually contains both hourly and salaried workers. This heterogeneity is not true, however, for the NIOSH group of salaried workers, which is comparable to the classification we used with Rocketdyne/AI workers. Most of the 8,363 employees labeled as salaried by NIOSH were drawn from only 4 occupational groups: formaldehyde- production workers (3,447), anatomists (2,317), petrochemical workers (1,472), and civilian workers at an airforce base (833) (see Table 4.1.b). Since NIOSH researchers had access to company personnel records for these cohorts, they were able to delete hourly workers. Thus, we believe that salaried workers in the NIOSH population are sociodemographically similar to the salaried workers at Rocketdyne/AI.

Many of the studies forming the NIOSH reference population were conducted to test specific hypotheses regarding the effects of occupational chemical exposures on cancer mortality. According to Zahm (1992), however, the wide variety of jobs, occupations, and industries represented in the total NIOSH population is supposed to result in risks of specific diseases that are typical of general working populations. Nevertheless, the risk of dying from certain cancers in the NIOSH population may still have been higher than would be expected if those workers had not been exposed to occupational carcinogens. Thus, our external comparisons of monitored workers with the NIOSH population may have underestimated the health risks of working at Rocketdyne/AI.

For this investigation, as in other studies of workers at nuclear facilities, the only practical source of information on cancer occurrence was death certificates. Although it would have been desirable to examine incidence, rather than mortality, only population tumor registries systematically compile information about all newly diagnosed cases of cancer in a given area, and the Southern California registries were established too late to cover most of the follow-up period for our cohort. Moreover, we have found that our study population has been relatively mobile, such that about a quarter of all cohort members have died out of state. Thus, cancer registries covering
all of California would probably have missed many of these cases.

We were not able to validate the cause-of-death entries on death certificates with information from next of kin or hospital and pathology records. As documented in the literature, such a "follow-back" investigation could improve the quality of mortality data (Ron et al., 1994a). Financial constraints and issues of confidentiality, however, prevented us from obtaining mortality information from any source other than death certificates.

The major methodologic problems of using death certificates alone to obtain information on cancer mortality are: inaccuracies in determining the specific cancer site, e.g., distinguishing between colon and rectal cancers; difficulties in determining whether a reported cancer site is the primary or a secondary malignancy; and underreporting of multiple primary cancers in the same individual. Underreporting of cancer as a cause of death, in general, is much more frequent for individuals over 70 years of age (32% of our deaths) and for those who did not die in a hospital. If the recorded cause of death is based on a biopsy or an autopsy, the diagnosis on the death certificate gains validity, but on only 10% of our death certificates was such a procedure noted.

In general, we would expect the misclassification of cancer as the cause of death on death certificates to be nondifferential with respect to radiation dose--i.e., the proportion of misclassified cancer deaths of a specific type and the proportion of misclassified deaths from other causes would not vary by level of radiation dose. Therefore, we would expect the direction of misclassification bias in effect estimation to be toward the null value (RR = 1). Since the frequencies of many types of cancer are small in our study, however, adding or subtracting only one death from a given dose category might change the results appreciably.

The latest comparison of cancer-incidence with cancer-mortality results for A-bomb survivors showed that, in general, cancer-incidence data provided more outcome events with which to assess a dose-response relationship, but cancer-mortality analyses did not produce fallacious trends when compared with the results of cancer-incidence analyses (Ron et al., 1994b). Demers et
al. (1992) compared results based on cancer-incidence data with those based on mortality information in an occupational cohort study of fire fighters and policemen. Consistent with Surveillance Epidemiology End Results data (Horm et al., 1985; Chu et al., 1990), these authors found many more incident than fatal cases for cancers of better prognosis, such as the oral cavity, pharynx, colon, rectum, prostate, bladder, and skin; but only for bladder and colon cancers did the mortality data produce effect estimates different from those based on the incidence data. Relative to the general population, the index cohort experienced a lower cancer-mortality rate, but the same incidence rate. The authors concluded that this difference between incidence and mortality was due to differential case fatality; i.e., cancer cases in the index cohort had a better survival than did cases in the general population, possibly due to better health-insurance coverage for fire fighters and policemen. We might expect such an effect for cancers with a low fatality rate in the Rocketdyne/AI cohort, as well, since Rocketdyne/AI employees had extensive health-insurance coverage.

Internal Comparisons: External-Radiation Effects

The Rocketdyne/AI workers monitored for external radiation experienced increases in mortality with increasing cumulative external-radiation dose for both total cancers and all solid cancers of so-called radiosensitive organs but not solid cancers of nonradiosensitive organs. In addition, we observed a clear increase in mortality from hemato- and lymphopoietic cancers at high doses ($\geq 200$ mSv). Such high levels were also associated with an elevation of lung-cancer mortality.

Our study population is one of the smallest among the nuclear cohorts investigated to date (see Table 1.1). As discussed in the Methods section, a dose-response analysis of many site-specific cancers was not feasible for the HPRMP cohort because of the small numbers of cancer deaths observed for most sites. In order to assess dose-response relationships, therefore, we combined target cancer sites, using a priori knowledge according to BEIR V (1990), into three groups:
cancers of the blood and lymph system (hemato- and lymphopoietic cancers excluding chronic lymphocytic leukemia), radiosensitive solid cancers, and nonradiosensitive solid cancers. We also conducted sensitivity analyses of our cancer groupings by including and excluding certain cancers; yet the results reported in Tables 3.8 and 3.12 did not change. Our finding of an association between external-radiation dose and mortality from radiosensitive solid cancers indicates that, in contrast to the results of certain previous studies (see Table 4.2), the trend observed for total-cancer mortality cannot be attributed solely to the effects on hemato- and lymphopoietic cancers. Furthermore, the magnitude of the effect of external radiation was similar for total cancers and radiosensitive solid cancers in our study.

Although our dose-response analyses are based on small numbers of cancer deaths, there are several pieces of evidence to suggest that some, if not all, of the observed trends are likely to represent true radiation effects. First, a dose-response analysis pooling all cancer deaths in our study that are not included in the "radiosensitive" categories showed no effect of radiation exposure, as expected. Second, the results of certain dose-response analyses (internal comparisons) are consistent with related findings from the external comparisons involving two different reference populations. Specifically, mortality rates for leukemias in our study population were elevated in comparison to each external reference population. Furthermore, the excess mortality rate of these cancers, relative to the NIOSH population, was restricted to salaried workers.

A third piece of supporting evidence for our major findings is that the cancer sites associated with external radiation in our study are consistent with findings of external-radiation effects from previous studies. In accordance with the pattern of high-dose effects in humans and animals, one would expect exposure to low-level external radiation to increase the risk of leukemias and cancers of organs with so-called radiosensitive tissues—i.e., tissues with immature, undifferentiated, and rapidly dividing cells. Previous studies of low-level exposures have partially borne out this prediction. For example, researchers at the International Agency for Research on
Cancer (IARC) conducted a pooled analyses of data from 7 published nuclear-cohort studies (Cardis et al., 1995). These investigators found an effect of low-level ionizing radiation on leukemia mortality, but the magnitude of this effect, though similar to the results of the A-bomb-survivor analyses, is smaller than the effect estimated for hemato- and lymphopoietic cancers in our study (see Table 4.2). Moreover, in contrast, to our findings, Cardis et al. (1995) reported no effects of radiation on cancers other than leukemias. We believe, however, that Cardis et al. did not adequately take into account the substantial heterogeneity of effect across studies. Indeed, the relatively small pooled effect they reported for leukemias was largely determined by the results of one large study (Hanford).

Gilbert (1989) pointed out that data from A-bomb survivors and from therapeutically irradiated ankylosing-spondylitis patients (Darby et al., 1985) have yielded the highest rate ratios for easily diagnosed cancers that occur in sufficient numbers to be studied adequately, rather than for those cancers characterized as highly radiogenic according to conventional biologic criteria for radiosensitivity. Furthermore, on the basis of empirical evidence from studies of medically irradiated patients, the authors of BEIR V (1990) classified the brain as a radiosensitive organ, although it does not meet the definition of a biologically radiosensitive tissue. Findings from occupational cohort and case-control studies suggest that radiation is not only associated with so-called radiosensitive cancers (e.g., lung, leukemia, and brain), but also with cancers not regarded as radiosensitive (e.g., prostate and some female genital organs). Increases in the risks of leukemia, multiple myeloma, and cancers of the lung, ovary, and urogenital system have also been reported for A-bomb survivors exposed to more than 200 mSv (Shimizu et al., 1990). Subsequently, however, the results for multiple myeloma were revised; according to the latest incidence data, there is no increased risk with increasing external dose (Preston et al., 1994).

One reason for inconsistent findings across studies may relate to differences in the time required for radiation to induce different types of cancer. For example, Checkoway et al. (1988)
found that the effect of radiation on lung-cancer mortality diminished with increasing lag in exposure measurement, a phenomenon also observed in our cohort. Thus, our lagged analysis suggested a stronger effect of external-radiation dose on lung cancers when we used shorter lags (5 years or less). Such findings may indicate a predominantly late-stage effect for radiation on lung cancers, if it is not an artifact due to the small numbers of deaths in both studies. In contrast, for total cancers and for hemato- and lymphopoietic cancers, lags of 15 to 20 years yield the largest rate-ratio estimates. Although it is best to perform lagged analyses with specific cancer sites, in our study there was sufficient information to perform such analyses only for lung cancer.

In the A-bomb survivor studies, deaths from leukemias peaked only 5 years after the exposure, while other cancers showed a much longer induction/latency (BEIR V, 1990). In addition, some leukemias tend to occur earlier in adult life than do other cancers. One might argue from those findings that radiation effects on solid cancers have not been observed consistently in previous occupational studies because the follow-up time in those studies was too short to allow for the longer induction/latency periods (> 10 years) required for the development of radiation-induced solid cancers (other than lung cancer). Shimizu et al. (1990) argue that there is no evidence that radiation-induced cancers appear earlier than other cancers at the same sites; rather, the increase in site-specific, radiation-induced cancer mortality occurs at approximately the same ages when cancer mortality from natural (background) sources increases. Thus, nuclear workers exposed in their twenties would have to be followed for as long as 30-40 years before a potential radiation effect could be observed. It is not surprising, therefore, that findings and conclusions from previous studies in the nuclear industry changed considerably with increasing duration of follow-up (see Table 1.4). Thus, the varying durations of follow-up in previous studies might be one reason for the inconsistency of published results.

The average follow-up time for members of the externally monitored Rocketdyne/AI cohort (26 years) is one of the longest reported in the literature to date. The resulting advantages are two-
In addition to allowing for longer periods of cancer induction/latency, the extended follow-up has enabled us to study a relatively high proportion of workers exposed late in life. Note that the effect on lung-cancer mortality of exposure to external radiation after age 50 is much greater than the corresponding effects of the same cumulative doses at younger ages (see Table 3.10a-b).

Internal Comparisons: Internal-Radiation Effects

Increases in mortality with increasing internal-radiation dose were found for hemato- and lymphopoietic cancers and upper-aerodigestive-tract cancers among Rocketdyne/AI employees. No effects were observed on mortality from urinary-tract cancers. Although an inverse association was found between internal-radiation dose and lung-cancer mortality, we do not regard a protective effect of radionuclide exposure to be biologically plausible. Thus, we believe that this latter association was probably a chance finding (p = 0.20); it may have resulted from negative bias due to unmeasured confounders.

Results from other studies have been inconsistent regarding the health effects of internal exposure from alpha-radiation-emitting particles in nuclear cohorts. Wiggs et al. (1994) reported a slightly elevated lung-cancer-mortality rate among plutonium-exposed workers at the Los Alamos National Laboratories. Checkoway et al. (1988) found the strongest gradient for the effect of cumulative (external) gamma-radiation dose on lung-cancer mortality in a subgroup of workers also exposed to more than 50 mSv of (internal) alpha radiation; but Dupree (1994) was not able to confirm these results in an extended follow-up of the same cohort. In British studies, trends for all cancers, lung cancer, and prostate cancer showed an increase in mortality with increasing dose of external radiation only among those workers who were monitored for both external and internal radiation (Beral et al., 1985; Beral et al., 1988).

We did not observe an effect of internal radiation on lung-cancer mortality in our cohort, in part perhaps, because of confounding by other risk factors. The most likely potential confounders
are smoking and chemical carcinogens such as asbestos and beryllium. We did not (and will not) have the information necessary to adjust properly for individual exposures to specific chemicals, but we were able to examine the smoking distribution for a subgroup of internally exposed workers. We did not find a consistent association between smoking and cumulative internal radiation dose; therefore, our results are not likely to be confounded appreciably by smoking.

As was true for external radiation, the results of certain dose-response analyses of internal radiation (internal comparisons) are consistent with related findings from the external comparisons involving two different reference populations. Specifically, mortality rates for leukemia in our study population were elevated in comparison to both the U.S. population and the NIOSH population of salaried workers. The implication is that the excess mortality rate of these cancers in the Rocketdyne/AI cohort appears to be due to the effects of low-level, internal and external, ionizing radiation.

Wilkinson et al. (1987) reported results for internal radiation that are similar to ours; they found that Rocky Flats employees with a positive plutonium body burden experienced increased mortality from hemato- and lymphopoietic cancers. Elevated rates of these cancers have also been observed in medical patients treated with high doses of Thorotrast (BEIR IV, 1988). In addition, consistent dose-response associations with leukemias have been observed for lower levels of exposure to alpha emitters. Archer et al. (1973) also reported an estimated SMR of 4 for these cancers among uranium miners and millers (based on only 4 cases, with 1 expected), and Waxweiler et al. (1983) found a small increase for lymphatic cancers among uranium millers (again based on small numbers).

A dose-response relationship between radiation and cancers of the upper-aerodigestive tract has not previously been described for occupational cohorts. The only finding of an association between internal alpha radiation and cancer was reported by Wilkinson (1985), who observed rates of gastric-cancer mortality that were higher in several northern New Mexico counties with
substantial deposits of uranium than in counties without such deposits. Those results need to be interpreted with caution, however, since they are based on ecologic (aggregate) data and since residents of the high-risk counties may also have been exposed to other carcinogens, such as arsenic and cadmium.

A positive association between internal-radiation dose and external-radiation dose in Oak Ridge workers was reported by Checkoway et al., 1988. This association was also observed in our study among monitored workers (see Tables 3.7 and 3.10). Thus, in all analyses of external-radiation effects, we adjusted for the effect of internal radiation, and vice versa. Our analysis of the combined effect of both exposures suggests an increase in total-cancer mortality with both types of radiation (Table 3.13.a-b).

The evaluation of alpha-radiation exposure in this study focused on the potential for damage due to physical contact with an organ or tissue while the radioactive particle is moving through the body. Accordingly, we grouped cancers according to the organs of radionuclide entry or exit, with a separate category for all cancers of the blood and lymph system. Use of these outcome categories in dose-response analyses of internal radiation has an important limitation, however, since most of the dose measurements were calculated on the basis of expected doses to the lung. Thus, very different doses might have been delivered to other organ systems, depending on the radioactive-decay process and the retention function of the radionuclide for different organs. According to our health physicist (DCB), the quality of our internal-radiation data does not allow us to calculate specific organ doses beyond lung doses. Nevertheless, we can still use our computed lung doses as crude indicators of dose to other organs.

The mean radionuclide lung dose in our cohort of 2,297 internally monitored workers was only 2.1 mSv. This dose is much lower, for example, than the average lung dose of 82.1 mSv reported for 3,491 workers of the Y-12 facility at the Oak Ridge National Laboratory (Checkoway et al., 1988).
We chose to exclude workers unmonitored for alpha-radiation exposure from all analyses of internal-radiation effects for two reasons: to minimize exposure misclassification, since some of the unmonitored workers were probably exposed to alpha radiation before 1963; and to minimize possible selection bias resulting from differences in unmeasured risk factors between monitored and unmonitored workers. Evidence for this second rationale comes from the work of Wilkinson and Morgenstern (1995), who found that mortality rates for several cancers in the Rocky Flats study differed markedly for unmonitored workers and monitored workers with near-zero levels of plutonium uptake. Consequently, the total number of cancer deaths observed in our analyses was reduced from 258 in the group monitored for external radiation to 134 in the group monitored for internal radiation.

Given the relatively low levels of internal radiation in our cohort and the relatively small number of cancer deaths, especially at high doses, we were somewhat surprised to find such pronounced dose-response associations with both hemato- and lymphopoietic cancers and upper-aerodigestive-tract cancers. On the other hand, the negative results for exit-organ cancers, such as those of the kidney and bladder might be misleading, because bladder cancer is relatively nonfatal; the ratio of mortality to incidence is 1:6. Mortality data might not reflect the effect of radiation exposure on the incidence of these nonfatal cancers if, for example, access to health care and therefore survival among cancer cases varied according to level of radiation exposure.

In summary, despite the small size of the group monitored for internal radiation, our finding of a dose-response association between cumulative internal-radiation dose and mortality from hemato- and lymphopoietic cancers is consistent across both phases of the analysis (external and internal comparisons), is widely regarded to be biologically plausible, and is consistent with the results of other studies. The dose-response association with upper-aerodigestive-tract cancers, though strong and biologically plausible, needs to be replicated in other populations.
Confounding and Effect Modification

The estimated rate ratios reported in this study have not been adjusted for smoking, a well-known risk factor for many of the cancers considered in our analyses. In order to confound the effect of radiation on cancer mortality, a covariate not only must be a risk factor for the disease, but also it must be associated with radiation dose in the total cohort. We examined the association between radiation dose and smoking during two periods for which smoking data were available from subgroups of our cohort. For those two periods, 1961-69 and 1980-94, we found that the distribution of smoking did not vary in any systematic way with cumulative dose of external or internal radiation. Thus, smoking is not likely to confound the effect of radiation dose on the risk of dying from any disease. Nevertheless, residual confounding due to smoking cannot be ruled out because of the lack of complete smoking histories in our subjects.

In a case-control study designed to address this confounding problem, Petersen et al. (1989) also showed that tobacco use was not strongly related to radiation dose among workers of the Hanford nuclear facility. Those authors also demonstrated that adjustment for smoking in the analysis did not appreciably change the estimated effects of cumulative dose on lung-cancer risk.

Since pay type (our indicator of socioeconomic status) was associated with smoking in the study population (see Tables 3.15, 3.17, and 3.19), we might have partially controlled for the effect of smoking on cancer mortality by adding pay type to our models. Furthermore, smoking prevalence for Rocketdyne/AI employees in the 1960s appears comparable to that of the general U.S. population of white males in 1965 (U.S. Surgeon General, 1979), and smoking prevalence is even lower for Rocketdyne/AI employees in the 1980s than for the general U.S. population of white males in 1980 (U.S. Surgeon General, 1983). Thus, neither the external nor internal comparisons in this study are likely to have been positively confounded by smoking.

Since radiation dose in our monitored study population may have been associated (perhaps inversely) with exposures to chemical carcinogens, it is possible that radiation effects were
confounded by the effects of these chemical exposures. To address this concern, we attempted to identify employees likely to have been exposed to chemical carcinogens at Rocketdyne/AI. Industrial hygienists working on our study surveyed the facility, interviewed managers and workers, and assessed the potential for exposure to chemical carcinogens by evaluating job titles according to location and period. We identified beryllium, asbestos, some solvents, and hydrazine as carcinogenic substances to which workers in our study population could have been exposed (Wagoner et al., 1980; Carpenter et al., 1988). We were unable to measure these exposures at the individual level, however, due to the lack of information on worker locations. Instead, we created two 4-category variables (none, potential, low, and high) for hydrazine and asbestos exposures from a crude job-exposure matrix based on available information. By adding binary covariates for these chemical exposures to the logistic models, we found that the estimated effects of radiation did not change appreciably. This apparent lack of confounding by these chemical exposures was observed for all cancer outcomes, including lung-cancer mortality. Although we observed a crude association between our asbestos measure and total external-radiation dose (see Table 2.10), this association ignores the time-dependent treatment of these covariates and the associations with other covariates in the model; in addition, the asbestos variable is only minimally associated with cancer mortality, including lung cancer. Thus, the effects of radiation reported in this study do not appear to be confounded by the effects of asbestos or hydrazine exposures. Nevertheless, because of the crude measurement, we cannot rule out residual confounding due to these or other unmeasured risk factors (e.g., solvents, diet, and alcohol).

Another factor that might be responsible for inconsistent results across occupational studies is potential modification of radiation effects by age at exposure. Kneale and Stewart (1993; 1995) reported that the effect of external radiation on total-cancer mortality at Hanford was much higher for workers exposed after age 58 than for workers exposed earlier in life. Indeed, their results indicated that a cumulative dose of only 10 mSv after age 58 could double the total-cancer mortality
rate (see also Table 4.2). The results of our analyses of radiation effects for cumulative doses received during three age intervals seem to corroborate Kneale and Stewart's finding of effect modification by exposure age (see Tables 3.10.a-b). Although our estimated effects are weaker than theirs, we also found that the effect of external radiation on total-cancer mortality was strongest for workers exposed after age 50. A similar pattern of effect modification was found for radiosensitive solid cancers, including lung cancer. In contrast, the opposite pattern was observed for hematopoietic cancers, such that the effect of external radiation was strongest for workers exposed before age 50. Given the imprecision of these effect estimates, however, our results must be interpreted cautiously.

5. CONCLUSIONS

All available evidence from this study indicates that occupational exposure to ionizing radiation among nuclear workers at Rocketdyne/Al has increased the risk of dying from cancers of the blood and lymph system. Despite the small numbers of deaths from these cancers in workers with relatively high doses, we observed associations for both external and internal radiation, and these associations are not likely to be chance findings; furthermore, these findings are consistent with the results of our external comparisons with two reference populations. In addition, these findings are consistent with results previously reported for several other nuclear cohorts.

Exposure to external radiation appears to have increased the risk of dying from lung cancer. Although this effect has not been observed consistently in other studies of nuclear workers, it does not appear to be due to the confounding effects of smoking, asbestos, or hydrazine exposures. Nevertheless, we cannot rule out residual confounding by these factors or by unmeasured risk factors such as other chemical carcinogens, but such potential bias could be in either direction.
Results of this study strongly suggest that exposure to internal radiation has increased the risk of dying from cancers of the upper-aerodigestive tract. We observed a strong dose-response relationship that is not likely to be a chance finding. Although there were limitations in measuring internal-radiation doses among workers, we would expect such measurement errors to result in an effect estimate that is smaller than the true effect (i.e., bias toward the null). Nevertheless, we cannot rule out confounding (in either direction) by alcohol consumption, dietary factors, and other unmeasured risk factors. Upper-aerodigestive-tract cancers have not been analyzed as a single group in previous radiation studies, and we did not have enough deaths of each cancer type in this group to conduct separate dose-response analyses; thus, our finding needs to be replicated in other populations. In contrast to findings reported for several other epidemiologic studies of radiation effects, we observed an association between cumulative external-radiation dose and total-cancer mortality. Indeed, the estimated excess rate ratio (rate ratio minus one) corresponding to the effect of 100 mSv was at least 6 to 8 times greater in our study than comparable estimates extrapolated from the study of A-bomb survivors (Tables 3.9 and 4.2). Our results, however, are consistent with those of two previous studies of nuclear workers.

We estimated that 9 cancer deaths observed in the externally monitored cohort were attributable to external-radiation doses of 10 mSv or more; this attributable number represents 3.5% of all observed cancer deaths and 11.1% of "exposed" cancer deaths with cumulative doses of 10 mSv or more. We also estimated that 15 cancer deaths observed in the internally monitored cohort were attributable to internal-radiation doses greater than 0 mSv; this attributable number represents 11.2% of all observed cancer deaths and 27.3% of "exposed" cancer deaths with cumulative doses greater than 0 mSv. Since we were not able to provide confidence limits for these estimates, their precision cannot be assessed. Nevertheless, the estimated numbers of attributable deaths may be conservative for several reasons: e.g., they ignore deaths possibly due to external doses less than 10 mSv; they ignore possible radiation-induced cancer deaths after 1994; and they
ignore radiation-induced cases of cancer that are not fatal.

The results of this study also suggest that the effect of low-level ionizing radiation may vary by age at exposure and that the pattern of this effect modification by exposure age may differ by type of cancer. While the estimated effects of external radiation on total cancers, radiosensitive solid cancers, and lung cancer were largest for doses received after age 50, the estimated effect on hemato- and lymphopoietic cancers was largest for doses received before age 50. Despite the low statistical power for testing the effects of age-specific radiation doses in our analyses, these results are consistent with findings from other studies. We therefore recommend that other researchers consider exposure age when estimating the effects of ionizing radiation.

Results of the external comparisons suggest that the mortality rates for all causes and, in particular, heart disease were lower for monitored Rocketdyne/AI workers than for either the general U.S. population or the NIOSH population of other worker cohorts. These findings do not mean that being employed at Rocketdyne/AI decreases the risk of dying from heart disease or other causes, but rather that healthier individuals are more likely to get employed at Rocketdyne/AI and stay in the radiation-monitoring program than are less healthy individuals. This latter phenomenon is known as the "healthy-worker effect."

Although we cannot rule out all forms of error in our estimates of radiation effects, we believe the direction of possible bias is no more likely to be away from the null (exaggerating effects) than toward the null (underestimating effects). Moreover, the positive findings observed in our study, in contrast to many previous studies, may be due in part to the extended follow-up period. Longer follow-up allows time for the development of radiation-induced cancers that are characterized by long induction/latency periods or that tend to occur more frequently after exposures late in life. It should be noted that only 20% of monitored workers had died by the end of the follow-up period. On the basis of this consideration, plus other methodologic issues that cannot be resolved by the present study, we recommend continued follow-up of the Rocketdyne/AI
cohort in the coming decades. Future surveillance should include the detection of cancer incidence as well as mortality.
REFERENCES


Committee to Bridge the Gap (1980).  Past Accidents and Areas of Possible Present Concern
Regarding Atomics International.  Committee to Bridge the Gap, Los Angeles.


Occupational Radiation Monitoring Data for Use in Epidemiologic Studies.  Oak Ridge Associated
Universities, Report No ORAU 89/A-127.


bomb survivors and patients with ankylosing spondylitis given x-ray therapy.  J Nat Cancer Inst
75:1-21.

versus death certificates in occupational cohort studies in the Unites States.  Am J of Epidemiol

exposure and lung cancer risk in four uranium processing operations.  Epidemiology 6:370-375.

autopsied population with specific attention to malignant neoplasms and vascular diseases.  Am J

Flanders DW, Cardenas VM, Austin H (1993).  Confounding by time since hire in internal


at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Nuclear Weapons Plant.

Gilbert ES, Fix JJ (1995).  Accounting for bias in dose estimates in analyses of data from nuclear


Monson RR (1994). Documentation accompanying the Monson program. Harvard School of Public Health, Boston, MA.


U.S. Department of Health and Human Services (1989). International Classification of Diseases,
9th Revision, 3rd ed. DHHS Publication No (PHS) 89-1260. USDHHS, Rockville, MD.


