

Report of Epidemiologic Analyses Performed for Rocky Flats Production Workers
Employed Between 1952-1989

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ABSTRACT

We identified a cohort of 16,303 production era workers employed at the Rocky Flats Plant for six months or more between 1952 and 1989, for whom we assembled data on dates of birth and hire, and vital status. For this cohort, we corrected data for annual external penetrating radiation doses, assembled data for systemic deposition of plutonium-239 and -240 and, with a job exposure matrix, estimated exposures to asbestos and nine toxic chemicals. Standardized mortality ratios (SMRs) for the production era cohort were significantly lower than expected for all causes of death and all deaths with cancer as an underlying cause. Elevated SMRs were noted for cancers of the stomach, rectum, brain and other central nervous system sites, connective and other soft tissue, as well as for unspecified neoplasms of the nervous system and unspecified anemias. The SMR for lung cancer was not elevated. Only the elevated SMR for unspecified neoplasms of the nervous system was statistically significant ($p < 0.05$) when Colorado mortality rates were used to compute the expected number of cases. Because of the strong healthy-worker effect and confounding by multiple variables, more analyses must be conducted to clarify relations between exposures and causes of death.

Matching the production era cohort with data from a statewide cancer registry identified some cancer sites that have larger numbers of incident cases than mortality cases. We are continuing to examine the strengths and weaknesses of analyses of cancer incidence for occupational cohorts.

We also conducted a nested case-control study to investigate associations between lung cancer mortality and lung dose from internal exposure to plutonium, americium, and uranium isotopes. Lung cancer deaths ($n=180$) were identified from death certificates and individually matched to 720 controls on birth date and gender, using incidence density sampling. We identified statistically significant risks for cumulative internal lung doses greater than 400 mSv, but estimates of risks for high dose categories were not stable, and were complexly influenced by a number of confounding variables. We identified age at first internal lung dose as a risk factor among workers with internal lung doses, with older workers being at higher risk than younger workers. Workers first hired between 1960 and 1967 were at significantly elevated risk and length of employment was inversely related to risk. No significant associations were found between lung cancer mortality and cumulative external penetrating radiation dose, or cumulative exposures to asbestos, beryllium, hexavalent chromium, or nickel. Although smoking frequency was a strong risk factor for lung cancer, this exposure did not confound the relation between cumulative internal lung dose and lung cancer.

Additional cohort-based analyses with improved internal dosimetry are needed to clarify the risks for lung cancer from internal exposures received by Rocky Flats workers. Such analyses will enable comparisons with data for Mayak plutonium workers in Russia, and help to clarify whether current radiation protection standards are adequately protective.

INTRODUCTION

This report provides a detailed summary of the methods and results of the epidemiologic studies of Rocky Flats workers performed through a cooperative agreement between the National Institute for Occupational Safety and Health (NIOSH) and the Colorado Department of Public Health and Environment, with collaboration from the Department of Preventive Medicine and Biometrics, University of Colorado School of Medicine. We report here on SMR estimates for the entire production era cohort and describe the incident cases of cancer identified by matching the cohort with a statewide cancer registry. We also report the results of a completed case-control study of lung cancer mortality, with estimates of annual internal lung doses and smoking frequency.

Rocky Flats production workers have been studied previously in a cohort mortality study of 5,413 white male workers employed for two years or more and followed between 1954 and 1979, with a total of 77,782 person-years (Wilkinson et al., 1987). Our study expanded the size of the cohort threefold by extensive searches of data sources and by including male and female production workers of all races and ethnicities employed for 6 months or more, and following them through the end of 1996. We also estimated exposures to chemical carcinogens for the entire cohort, and determined cumulative internal lung doses and histories of cigarette smoking for subjects in the lung cancer case-control study.

Recent studies of plutonium workers at the Mayak facility in Russia have identified associations between exposures to plutonium isotopes and increased risks for cancers of the lung, liver, and the combined sites of bone and connective tissue, as well as hematopoietic and lymphatic malignancies. Studies of plutonium workers in the United States and England have not found such increases. The relationship between plutonium exposure and cancers noted in Mayak workers is consistent with what is known about the distribution of plutonium in the human body and resulting internal doses, as well as with results of studies of animals exposed to plutonium. Mayak workers, however, received much higher exposures to plutonium and external radiation than their counterparts in the United States and England.

The discrepancies between epidemiologic studies of plutonium workers might be explained either by the cancer risks per unit dose being low enough to be missed by epidemiologic studies of the U.S. and British workers, or by the use of estimates of exposure that were insensitive to low levels of risk. Studies of plutonium workers at U.S. facilities with improved estimates of exposure and dose may help answer these questions.

PLUTONIUM AND CANCER RISK

Animal Studies

The carcinogenic effects of plutonium have been well established in animal studies. These studies have consistently reported excesses of lung cancers, osteogenic sarcomas, primary liver carcinomas, bile duct tumors and lymphomas in dogs (Bair and Thompson, 1974; Muggenberg et al., 1996; Park et al., 1997; Grogan et al., 2001).

Gilbert et al. (1998) conducted a combined analysis of 260 beagle dogs and estimated age-specific risks for the incidence of lung, bone, and liver cancers. For lung tumors, a linear model provided an adequate fit for doses less than 20 Gy, and a linear-quadratic model adequately fit all data. A linear model also adequately fit the data for liver cancer. The dose-response model for bone cancer was nonlinear, and there was evidence for radiation-induced bone tumors at doses less than 0.5 Gy.

Hahn et al. (1999), in a study of beagle dogs, found an increase in lung cancer rates for dogs that received doses of 2 Gy or higher from plutonium-239 oxide.

Studies of rats have also produced evidence of lung cancer following lung doses above 1.5 Gy (Sanders et al., 1993; Oghiso et al., 1994; Lundgren et al., 1995).

In summary, there is strong evidence from animal studies of a causal relation between exposure to plutonium-239 and cancers of the lung, liver, and bone. Data on cancer risk per unit dose vary between species and between cancer sites (Grogan, et al., 2001).

U.S. Plutonium Workers

Reyes et al. (1984) were the first to publish on cancer in plutonium workers at the Rocky Flats Plant. They conducted a case-control study of brain tumors—a follow-up of preliminary cohort analyses that showed an excess risk for deaths from this cause. They found no relation between brain tumors and systemic deposition of plutonium (also termed body burden [Ruttenber et al., 2001]), external doses of ionizing radiation, job category, or work area.

Wilkinson et al. (1987) conducted a cohort study of the mortality of 5,413 white male workers who had been employed at Rocky Flats for a least two years between 1952 and the end of 1979. The average duration of follow-up for each worker was 14.5 years. For the entire cohort, standardized mortality ratios (SMRs) for all causes, all cancers and most other individual cancer sites indicated that mortality rates in the Rocky Flats cohort were lower than expected. However, a significantly elevated SMR (SMR=3.76, 95% confidence interval (CI) 1.77, 7.07) was reported for benign and unspecified neoplasms. Upon review of the death certificates, all seven of these neoplasms were found to be intracranial tumors.

Rocky Flats workers were stratified by systemic deposition of plutonium and external radiation dose and rate ratios were computed based on a stratified (by age and calendar period) maximum likelihood estimate of the rate ratio using person-years of exposure. For external doses, workers with a cumulative lifetime equivalent dose of ≥ 10 mSv were compared with workers with cumulative doses <10 mSv. For internal exposures to plutonium isotopes, systemic depositions of ≥ 74 Bq were compared to those <74 Bq.

Various induction periods (time elapsed from the first measurement of a cumulative external dose of 10 mSv or a systemic deposition of 74 Bq) were used in analyses of rates and rate ratios stratified by external dose and systemic

deposition. The induction periods were treated as unexposed person-time in analyses, producing effects similar to those of dose lagging.

Wilkinson et al. (1987) found non-significantly elevated rate ratios for all causes of death (RR=1.14, 95% CI 0.91, 1.43) and all lymphopoietic neoplasms (RR=7.69, 95% CI 0.99, 72.93) when employees with internal depositions of plutonium ≥ 74 Bq were compared with workers with depositions < 74 Bq), while accounting for age, calendar year, and a two-year induction period. Non-significant increases in the rate ratios with a two-year induction period were also noted for digestive system cancers (esophagus, stomach, and colon analyzed separately), lymphosarcomas and reticulum cell sarcomas (analyzed together), and prostate cancer.

Using a five-year induction period to categorize plutonium-exposed and unexposed workers, rate ratios for all causes (RR=1.33, 95% CI 1.05, 1.68), and all lymphopoietic neoplasms (RR=9.86, 95% CI 1.26, 94.03) were significantly elevated. With a ten-year induction period the rate ratio for mortality from all causes was significantly elevated (RR=1.39, 95% CI 1.04, 1.87), while no other rate ratio was significantly greater than one.

When comparing workers with cumulative external doses ≥ 10 mSv to those with doses < 10 mSv, non-significantly elevated rate ratios were reported for myeloid leukemia, lymphosarcoma and reticulum cell sarcoma, liver tumors and unspecified brain tumors. With a two-year induction period, rate ratios were higher but still not statistically significant for all lymphopoietic cancers and unspecified brain tumors. Compared with analyses for a two-year induction period, the rate ratios for all lymphopoietic cancers were lower for five- and ten-year induction periods; the rate ratio for unspecified brain tumors for a five-year induction period was higher, but the rate ratio for a ten-year induction period was lower. Excluding plutonium-exposed workers from the above analyses produced similar results, suggesting that the observed effects were associated with external penetrating radiation.

Dose-response relationships were analyzed between mortality and both internal deposition and cumulative external dose categories using least squares weighted regression, comparing directly adjusted rates among the systemic deposition and dose categories. No statistically significant trends for either external or internal exposure groups were observed. Increases in the standardized rate ratios (SRR) for internal deposition and all causes of mortality were observed with five- and ten-year induction periods, and for all cancers and all digestive cancers with a five-year induction period. For external dose, increases were observed in SRRs, with increasing exposure categories for all lymphopoietic neoplasms with a two-year induction period, and unspecified brain tumors with two- and five-year induction periods.

Wilkinson et al. (1987) had less than 49% power to detect a rate ratio of 2.0 for lung cancer when plutonium systemic deposition was dichotomized to levels ≥ 74 Bq and < 74 Bq ($\alpha = 0.05$). The mean follow-up of 14.5 years may

also have affected their ability to detect an elevated risk, as the latent period for radiation-induced cancers may be as long as 40 years.

Wiggs et al. (1994) published a mortality study of a cohort of former Manhattan Project workers and nuclear weapons workers at the Los Alamos National Laboratory (LANL). The study population comprised 15,727 white males who were first hired between 1943 and 1977 and followed through 1990. There was no restriction on employment duration and the average length of follow-up for a subject was 29 years. Of this group, 3,775 were monitored at some time for exposure to isotopes of plutonium, and 303 were considered exposed by the criterion of having an estimate of systemic deposition ≥ 74 Bq. For analyses with estimates of plutonium systemic deposition, a 10-year induction period--as defined by Wilkinson et al. (1987)-- was used. For analyses with external doses, the doses were lagged by a 10-year interval for solid tumors and 2 years for lymphopoietic and hematopoietic cancers.

Standardized mortality ratios for all causes and all cancers calculated with U.S. rates were significantly lower than 100. In comparisons of plutonium-exposed and unexposed workers, there were no significant elevations in rate ratios. However, the rate ratio for lung cancer was 1.78 (95%CI=0.79-3.99), based on 8 cases of lung cancer among the 303 plutonium-exposed workers. This study had less than 37% power ($\alpha = 0.05$) to detect a rate ratio of 2.0 for lung cancer with plutonium exposure treated as a dichotomous variable (≥ 74 Bq vs. < 74 Bq).

Analyses of dose-response relationships for external radiation doses resulted in statistically significant trends in rate ratios for Hodgkin's disease (2-year lag period), malignant neoplasms of the brain and central nervous system (10-year lag period), and cancer of the esophagus (10-year lag period). When plutonium-exposed workers were omitted from the analysis of external doses, dose-response trends for Hodgkin's disease, cancers of the brain and CNS and cancer of the esophagus were stronger and remained statistically significant. Additionally, rate ratios computed with a 5-year lag period for workers unexposed to plutonium were significantly elevated for cancer of the kidney and lymphocytic leukemia.

Voelz et al. (1979, 1985, 1991, 1997) followed 26 Manhattan Project workers, who were involved in the original plutonium research and weapons development. All 26 of these workers were included in the cohort analysis of Wiggs et al. (1994). By the end of 1994, seven workers had died--one of lung cancer, and one of osteosarcoma. Two were diagnosed with lung cancer, but had not died by the end of the follow-up period.

British Plutonium Workers

Omar et al. (1999) described the mortality through 1992 for 14,319 workers employed at the Sellafield plant between 1947 and 1975. They computed SMRs for plutonium workers, other radiation workers, non-radiation workers, and all workers, regardless of exposure status. Organ-specific doses from internal exposures to plutonium were estimated for several sites including

lung, liver, and, bone, and combined with external doses to evaluate mortality trends for plutonium workers over seven dose categories.

Cancer mortality rates for all radiation workers were 4% lower than those for England and Wales, but cancer mortality rates for plutonium workers were similar to those for this comparison population. Statistically significant excesses in mortality in the cohort of radiation and non-radiation workers were reported for cancers of the pleura and thyroid. The mortality from thyroid cancer, however, was not related to external radiation dose. Comparisons of cancer SMRs between plutonium and other radiation workers indicated a significant excess for only cancers of the female breast and ill-defined and secondary sites.

Omar et al. (1999) stratified mortality rates by both cumulative external radiation dose and by cumulative combined plutonium and external doses, and performed tests for trends with different lag periods. For all radiation workers, statistically significant trends of mortality rates with cumulative external radiation doses were reported for all causes of death (20-yr lag), ill-defined and secondary cancers (10-yr lag), leukemia (excluding chronic lymphatic, no lag and 2-yr lag periods), multiple myeloma (20-yr lag), and all lymphatic and hematopoietic cancers combined (20-yr lag).

When cancer incidence was analyzed for all radiation workers, there were statistically significant positive trends with cumulative external radiation dose lagged by 20 years for cancers of the brain and CNS, non-Hodgkin's lymphoma, and all lymphatic and hematopoietic neoplasms combined. The authors also reported a statistically significant trend in lung cancer incidence with cumulative dose from the sum of external and internal doses (no lag period) and for a group of plutonium workers that excluded workers who had internal doses estimated with urinalysis data that were suspected to be in error.

When trends were assessed for organ-specific plutonium dose alone, there were significant positive trends for all lymphatic and hematopoietic neoplasms combined (no lag period) and cancer of the pancreas (10-year lag).

The authors speculated that there may be evidence for a relationship between external radiation dose and multiple myeloma. They concluded that their findings did not suggest that plutonium workers had risks for cancer that were different from other radiation workers, or from the general population.

Russian Plutonium Workers

A number of studies of radiation exposures and cancer and other diseases have been conducted with data for workers at the Mayak facility in Russia. Koshurnikova et al. (1994) identified an increase in ratios of observed to expected mortality rates from hematopoietic and lymphatic malignancies in workers at a radiochemical processing plant. They also described proportionate mortality data for other malignancies. The ratio for mortality from stomach cancer in nuclear reactor workers was higher than noted for the USSR average, and the proportion of hematopoietic and lymphatic malignancies was also higher for workers at both reactor and radiochemical processing facilities.

Koshurnikova et al. (1996) calculated cancer SMRs for a cohort of Mayak workers exposed to plutonium isotopes and external gamma radiation. Standardized mortality ratios were calculated with a comparison group composed of other workers whose external doses did not exceed maximum permissible doses. All-cancer mortality was significantly elevated in both men (SMR=1.43, 95% CI 1.28, 1.60) and women (SMR=1.46, 95% CI 1.18, 1.82). Mortality for leukemia was significantly elevated in men (SMR=2.14, 95% CI 1.22, 3.70). Lung cancer SMR's for men in the plutonium production facility (SMR=3.33, 95% CI 2.23, 4.96) were twice as high as those for all male radiation workers (SMR 1.89, 95% CI 1.54, 2.32). Lung cancer SMRs for women in the plutonium production facility (10.39, 95% CI 2.78, 38.79) were about three times those for all female radiation workers (3.25, 95% CI 1.60, 6.63). When considering only those workers with plutonium body burdens, SMR's for lung cancer increased to 5.33 (95% CI 2.82, 10.07) in men and 16.92 (95% CI 2.14, 133.57) in women.

In a lung cancer case-control study of Mayak workers, Tokarskaya et al. (1995) found that cases were significantly more likely than controls to have had internal depositions of plutonium greater than 5.6 kBq (OR=3.2, 95% CI 1.8, 5.1). By using a cutoff for internal depositions of 0.75 kBq for exposed and unexposed plutonium workers, the OR for lung cancer was 1.3 and not statistically significant. Other risk factors that were significantly associated with lung cancer were smoking (OR=4.0, 95% CI 3.2, 13.7), decreased body mass (OR=1.9, 95% CI 1.1, 2.6), and a diagnosis of plutonium pneumosclerosis (OR=4.7, 95% CI 1.8, 11.9).

Khokhariakov et al. (1996) performed a dose-response analysis of lung cancer mortality in relation to cumulative radiation dose to the lung from internal and external exposures in the cohort described by Tokarskaya et al. (1995). The authors fitted mortality and dose data to a linear, no-threshold, relative risk model. External doses were measured with film badges and internal lung doses were estimated with urine bioassay data. Excess relative risk for lung cancer from chronic radiation exposure at Mayak was estimated to be 1.9 per Sv.

Tokarskaya et al. (1997) reported that a non-linear quadratic model with a threshold of 0.79 Gy best described the data previously reported by Tokarskaya et al. (1995). The use of this model with poorly documented plutonium dose estimates were questioned by Beyea (1998) and Khokhryakov et al. (1998). Because internal lung doses and smoking rates differed substantially between male and female workers, Khokhryakov et al. (1998) re-analyzed data from Tokarskaya et al. (1997) for men and women separately, and determined that a linear dose-response model best fit the data.

Koshurnikova et al. (1998) conducted a cohort study of 1,479 plutonium-exposed male workers hired between 1948 and 1958. They computed lung cancer SMRs with an internal control group (other Mayak workers whose body burdens did not exceed the maximum permissible activity of 1,480 Bq) and with national mortality rates. The lung cancer SMRs were significantly elevated for plutonium workers aged 50 and older. Standardized mortality ratios were also stratified by alpha-particle dose to the lung. Significantly elevated lung cancer

SMR's were reported for workers with alpha particle doses to the lung between 7 and 29 Sv.

The authors used a linear dose-response model to estimate lifetime excess relative risk (ERR) for lung cancer from plutonium lung doses below 30 Sv. The ERR was estimated at 1.21×10^{-2} per Sv. Because so little data existed for workers with doses greater than 30 Sv, the investigators considered estimates in that range unreliable.

Kreisheimer et al. (2000) studied a cohort (n=1,669) of plutonium-exposed, male Mayak workers. They computed lung cancer SMRs with an internal comparison group composed of other Mayak workers who were not exposed to plutonium, and examined dose-response relations with a linear model. The excess relative risk for lung cancer was estimated to be 0.27 per Gy for gamma doses; for alpha-particle dose, the excess relative risk for lung cancer at age 60 was 0.6 per Sv. The authors concluded that of the 191 lung cancer cases in Mayak workers, 98 (51%) could be attributed to radiation exposures at the facility, and 93 (49%) could be attributed to other causes. According to the model, of the 98 lung cancers attributable to radiation exposures, 23 (12%) were due to exposures to gamma radiation and 75 (39%) were due to plutonium exposures.

Koshurnikova et al. (2000) conducted a cohort mortality study of bone and connective tissue cancers in Mayak workers. The authors included selected soft tissue neoplasms (ICD-9 code 171)—specifically fibrosarcomas and synovial sarcomas but not myosarcomas. They used a Poisson regression model and stratification of external radiation exposure by two categories of cumulative lifetime dose and stratification of plutonium body burden by three categories. They identified excess mortality from bone and connective tissue cancers for workers with elevated body burdens of plutonium that exceeded 7.4 kBq, and for plutonium workers who were not routinely monitored. They did not detect elevated mortality for workers who had lower body burdens, possibly due to the practice of considering workers with burdens less than 0.26 kBq as having had body burdens of zero. They also identified a statistically significant linear relationship between risk and plutonium body burden modeled as a continuous variable.

Gilbert et al. (2000) used methods similar to those of Koshurnikova et al. (2000) to study liver cancers in Mayak workers. They identified high relative risks for workers exposed to body burdens in excess of 7.4 kBq and for plutonium workers who were not routinely monitored. They also detected a statistically significant relation between increasing risk and increasing body burden—particularly for female workers.

Summary of Epidemiologic Studies

Studies of Mayak workers have provided strong evidence for causal associations between plutonium exposure and cancers of the hematopoietic and lymphatic systems, lung, liver, bone and connective tissue, as well as for mortality from all cancers. The challenge at this point with regard to studies of

Mayak workers is to refine estimates of risk per unit dose of plutonium exposure, making sure to account for contributions from gamma and neutron doses.

Studies of U.S. and British plutonium worker cohorts have identified suggestive relations between a number of cancers and both internal and external radiation exposures. There is need for additional studies of the cohorts with evidence of associations between exposure and disease in order to determine whether the risks noted for the highly exposed Mayak workers can be detected in workers with lower exposures. Such data can help determine whether radiation protection standards adequately protect plutonium workers.

HISTORY OF THE ROCKY FLATS PLANT

The Rocky Flats Plant, located 16 miles northwest of Denver, began production of nuclear weapons components in 1952. Since construction of the plant in 1951 until 1989, approximately 23,000 workers were hired; the workforce included metal workers, chemical process operators, health physicists, chemists, engineers, machinists, radiological protection engineers, guards and office workers. Over 18,000 of these workers were monitored at some time for exposure to radiation. The plant has had four prime contractors: Dow Chemical (1951-1975), Rockwell International (1975-1989), EG&G, Inc. (1990-1995), and Kaiser-Hill (1995 - present).

Plutonium processing ceased in 1990 when the production of the Trident II missile was stopped. Since then, Rocky Flats (now called the Rocky Flats Environmental Technology Site [RFETS]) has been in the process of decommissioning and decontaminating the plant site. The completion of decommissioning is slated for 2006.

The fabrication of plutonium pits—the primary production activity at Rocky Flats—required both metallurgic and chemical processing. These processes include recycling plutonium metal into plutonium dioxide, conversion of plutonium dioxide to a metal in reduction furnaces, and rolling and machining the metal (Makhijani et al., 1995). Uranium and beryllium were also used in the production of the pits.

Working with plutonium was extremely dangerous because, aside from its toxic and carcinogenic properties, plutonium metal is pyrophoric. In September 1957, the first of hundreds of plutonium fires occurred (Ackland, 1999). In May of 1969, a fire larger than the one in 1957 spontaneously ignited from plutonium in a glove box used for plutonium part fabrication. The fire was able to burn for several hours undetected because of the ventilation system in the glove box.

Between 1966 and 1969, the plant's fire department responded to 164 fires, 31 of which were started by plutonium spontaneously igniting. During one incident in 1965, 400 workers received radiation doses from plutonium as a result of a fire that started in a clogged drain (Ackland, 1999). From 1961 through 1971, production operations were substantially increased in order to manufacture a new weapons component (details of this component are still classified). Production of this component (referred to as the Part V expansion) reportedly resulted in increased radiation exposures to workers, particularly from neutrons.

Workers at Rocky Flats had the potential to receive internal exposure to several plutonium isotopes (Pu-238, Pu-239, Pu-240, and Pu-241, which henceforth are collectively termed plutonium), americium-241, uranium-234 and uranium-238 by several modes: chronic inhalation, acute inhalation, and wound contamination. Americium-241 is produced through neutron capture by plutonium-239 and plutonium -240, and is always a contributor to internal dose from exposure to weapons-grade plutonium. Uranium-234 and uranium-238 were used in weapons components manufactured for a period in the 1960s.

Some workers have received well-documented, high-level intakes of plutonium and other radionuclides. For others, the documentation of intakes was poor or absent, especially for low-level intakes or those that occurred early in the plant's history. Organ-specific dose estimates are the preferred measure to use in evaluating health effects because the organs and tissues in which plutonium deposits are retained are the ones that will be exposed to the carcinogenic alpha particle emissions.

RESEARCH OBJECTIVES

Cohort Database

Reviews of available data for Rocky Flats workers indicated there was no single database that listed all former and current workers. We determined that data for annual doses from external exposures to gamma radiation were available for most former production workers, but annual doses were sometimes missing or combined over multiple years. Data for doses from external exposures to neutrons were incorrectly estimated for some years, and combined with gamma doses for some time periods. Data for internal exposures to radionuclides were only available in hard copy format.

Data for chemical exposures were not available except for some area-based air samples for beryllium collected in the later years of production. In order to conduct epidemiologic studies, we sought to develop a comprehensive database for all former production workers—one that would include all available data on demographic characteristics of workers, employment duration, job titles, descriptions of job tasks, radiation doses, and chemical exposures.

Cohort-Based Cancer Mortality Studies

Standardized mortality ratios (SMRs) can provide an overview of cancer mortality in an occupational cohort. Past studies of nuclear workers have identified strong healthy-worker effects that render simple SMRs ineffective in determining risks from toxic exposures. In this report, we present SMRs for the production worker cohort. We are also completing cohort-based mortality analyses for selected cancer sites stratified by internal and external doses. The results of these analyses will be reported as they are completed.

Cancer Incidence Studies

Cancer incidence studies can assess exposure-disease relations for cancers that are not usually fatal. They also provide additional subjects for case-

control analyses. A serious limitation of cancer incidence studies is the potentially large number of subjects who are lost to follow-up because they have left employment and there is no information on their residence within the time and space boundaries for registry reporting. Epidemiologic studies of cancer incidence in occupational cohorts have either considered workers who have left employment to be lost to follow-up, or attempted to determine eligibility for cancer registration with the addresses of subjects with administrative data such as drivers license or motor vehicle registration databases. Studies in countries with comprehensive national registries have not had this limitation.

As the first step for conducting cancer incidence studies of Rocky Flats workers, we matched the personal identifiers in the cohort database with the records of the Colorado Central Cancer Registry (CCCR) to determine the number of incident cases of cancers that will be available for future cohort and case-control studies. After initiating the epidemiologic study, we began a medical surveillance program for former production workers, which allowed us to determine the most recent addresses for production workers—data that will substantially improve the power and validity of incidence analyses and will allow us to compare the results from incidence analyses that employ intensive searches for eligible subjects with studies that censor the person-years of subjects after they leave employment. We have recently completed analyses of the impacts of censoring on standardized incidence ratios (SIRs) and produced estimates of SIRs for the cancers assessed in the mortality study. These results will be reported shortly.

Lung Cancer Case-Control Study

Although our research was designed before the publication of epidemiologic studies of lung cancer in Mayak workers, we had assigned highest priority to assessing the risk for lung cancer in plutonium-exposed workers. This determination was based on evidence for plutonium distribution in exposed humans and studies of animals exposed to plutonium via inhalation. We determined that the lung cancer risk for plutonium exposure would be best assessed by a case-control study of lung cancer mortality with careful reconstructions of internal doses to the lung. We designed a case-control study for lung cancer mortality that involved modeling annual lung doses with data obtained from dosimetry records for case and control subjects. We also designed a telephone survey to obtain smoking histories of case and control subjects.

METHODS

Production Worker Databases

We contacted all organizations that may have retained data relevant to an epidemiologic study and requested copies in electronic or hard-copy format. We used these data to construct an electronic database with records for individual production era workers.

A database was acquired from LANL that had been maintained for 9,539 production workers who were ever employed at Rocky Flats between 1951 and 1979. This database was originally constructed for the epidemiologic studies of Wilkinson et al. (1987). LANL had updated the vital status for this group through 1993, and had retrieved and coded death certificates for the deceased. This database contained name, maiden name, employee identification number (EID), dates of birth, hire, termination, and death, the date a person was last known to be alive, state of birth, and underlying cause of death coded according to the International Classification of diseases, 9th Revision (ICD-9). This database was reported to be relatively accurate and all fields except the date of death were used in construction of the cohort database.

Records for 14,327 former or current workers were obtained from the RFETS Personnel Offices. This file contained name, EID, social security number (SSN), dates of birth, hire, termination and death, last job title, and last-known home address. These data were reported to be of reasonable quality and all fields, except date of death (which was not reliable according to RFETS personnel), were used in construction of the production-era cohort database.

The nine databases that compose the Radiological Health Records System (RHRS) were obtained from the RFETS Radiation Protection Division. These databases were used both to identify workers for inclusion in the production era database and to link dosimetry data to individual workers. Three of these databases contained personnel information, including name, person-ID, SSN, date of birth, sex, last known address, telephone number, dates of hire and termination. Person-ID is a unique personal identification code that was reportedly assigned only once to each employee. This identification code was useful because other personal identifiers such as SSN and EID were sometimes shared by married couples, were assigned to more than one worker, or were inaccurately recorded. Person-ID was the unique identifier used to link personnel data to the radiation databases. The RHRS databases were considered to be of good quality and all fields were used in construction of the production era database.

The Rocky Flats Beryllium Health Surveillance Program (BHSP), which began in June 1991, has attempted to identify and contact all current and former employees of the DOE at Rocky Flats, its prime contractors, and subcontractors at Rocky Flats to obtain information about exposure to beryllium and evaluate each for signs of beryllium disease. A database of 23,196 records was obtained from the BHSP. This database contained employee name, EID, SSN, last known address and telephone number, dates of birth, hire, termination, and death, and vital status.

Because much of the data from the BHSP were found to be unreliable, only name, EID, SSN, date of birth, and address were used in the construction of the production era database. Vital status data from the BHSP were not used in the roster because programmers at RFETS reported that several hundred dates of death had been lost and could not be identified or retrieved. Addresses and

telephone numbers from this source were used to help locate next of kin for the smoking history interviews.

In 2000, we matched the cohort database with the radiation dosimetry database maintained by the Radiation Protection Division at RFETS and identified a group of 2,448 production-era workers who were not in the cohort database. These workers had been monitored for radiation exposure, but were not listed in any of the other databases developed for our study. The group is composed of contractors and Department of Energy employees who performed tasks that placed them at risk for internal and external radiation exposures; for this reason they were added to the production era database.

When discrepancies in data from different sources were identified, the value that appeared in the majority of the databases was retained for the production era database. If all databases had different values for a field, other Rocky Flats employee files, which were available in hard-copy format, were used to help reconcile discrepancies. The hard-copy data included the employee card files from the Radiation Protection, Health Effects, and Personnel Divisions at RFETS. We used data from the dosimetry databases described below to estimate dates of hire or termination that were missing from the sources noted above.

Although no historical data exist regarding the specific job tasks performed by contractors, both internal and external radiation dose data exist for most of the contractors. Because many contractors had records of exposures to internal and external radiation, they were retained in the production era database.

Quantifying Exposures for Production Workers

Doses From External Penetrating Radiation

Data for external radiation doses came from film and thermoluminescent dosimetry (TLD) badges that measured total body doses from external gamma and neutron exposures. Six separate radiation databases were obtained from the Radiation Protection Division at Rocky Flats. Two databases recorded the external doses measured by personal dosimeters. The first contained quarterly doses recorded from 1991 to 1996 and the second, combined annual doses recorded for individual workers for all exposures occurring before December 31, 1976 and doses for individual workers recorded for variable time periods from January 1, 1977 through December 31, 1990.

In both databases, individual records identified by badge number recorded the dose for the period over which a personal dosimetry badge was worn. Badge reading intervals varied from quarterly to annual periods, but were usually quarterly. The two databases were combined, yielding a total of 521,778 records. The electronic databases recorded separate doses from gamma photons and neutrons for 1959-1963 and for all years after 1975. For 1952-1958 and 1964-1975, only total penetrating dose—the sum of equivalent doses from gamma photons and neutrons—was recorded electronically. For 1976, a large number of neutron and gamma doses were erroneously recorded—apparently due to mistakes made in updating the computer data system.

Data for annual external radiation doses were also obtained from LANL for the cohort of 9,539 workers that was established by Wilkinson et al. (1987). These data were compared with data from other sources for quality assurance, and used when external doses were missing from other sources.

Correcting Neutron Doses

From the beginning of plant operation, neutron exposure from the fluorination of plutonium was monitored with ionization chambers in order to estimate dose ranges and identify work areas with neutron exposures. Film-badge personal dosimeters were also used to estimate doses for individual workers. From 1952 to 1975, neutron doses were estimated with film dosimeters by physically counting neutron tracks with light microscopy. For the period 1952-1966, too few microscope fields were counted to yield accurate dose estimates—resulting in a systematic underestimation of neutron doses for this period.

From 1967 to 1973, film badge dosimeters continued to be used, but with improved counting methods and a program of quality assurance. TLD personal dosimeters measured neutron dose for some workers starting in 1971, and for all workers by 1973. As mentioned above, electronic records of neutron doses for 1976 contain erroneous doses, and have been imputed with methods described below. From 1977 to the present, neutron doses have been reported separately from gamma doses, and added to gamma doses to produce total penetrating doses. For all years, a quality factor or a relative biologic effectiveness of 10 was used to convert absorbed dose to equivalent dose for neutron exposure.

Because computer databases for dosimetry have recorded total penetrating doses (the sum of equivalent doses from gamma photons and neutrons) for most workers between 1952 and 1975, it is not possible to directly extract the erroneous neutron doses from the electronic data for these workers. There are electronic records with separate gamma and neutron doses for some workers from 1952 to 1970. Analyses of ratios for accurate gamma and neutron doses between 1968 and 1971 indicate that neutron doses for Building 771 (the site of plutonium fluorination processes) were about two times as high as gamma doses for the years between 1952 and 1966, and one-half as high as gamma doses for the other buildings where neutron exposures occurred during this time period. We used these ratios and data on administrative building assignments and job titles to adjust neutron doses for workers with separate neutron and gamma doses.

We used these adjusted neutron doses and presumably correct neutron doses from 1977 to 1989 to estimate “correction ratios” for total penetrating doses—the ratios of neutron-adjusted total penetrating dose to total penetrating dose for all workers with recorded neutron doses for building 771 (mean of ratios = 1.99, standard deviation [SD] = 0.92), and for other buildings (mean of ratios = 1.13, SD = 0.82). We then used the neutron dose data and the JEM to identify all buildings that had neutron exposures, and computed corrected total penetrating doses by applying the correction ratios to total penetrating dose for

the workers in these buildings who did not have separate neutron doses recorded for the years 1952 to 1966.

Imputing Missing Data for External Penetrating Doses

Quality assurance for external dose data was performed by checking dates of hire and termination against the dates of recorded doses in the electronic dosimetry files and reviewing health physics records for incident reports when workers with unusual doses were identified. These procedures identified individual workers for whom dose records were missing or apparently incorrect.

The 'nearby method' was used to estimate annual external penetrating doses for workers with missing or incorrect dose data for specific years of employment. This method, described by Richardson et al. (1999), and Ruttenber et al. (2001), imputes doses by using the mean of the existing doses for the individual worker within two years before and two years after the missing year. For strings of five or more years of missing external penetrating dose, notional doses were computed using the JEM to identify mean annual doses for other workers with similar job titles and work locations. If JEM data were not available, annual geometric means for all workers were used. Doses of zero were assigned for missing data as an alternative to the nearby method, and separate analyses were performed with these data.

Internal Exposures to Radionuclides

The majority of radionuclide intakes for Rocky Flats workers were from inhalation and wound contamination exposures to plutonium-239 and plutonium-240. Workers also received intakes of plutonium-238, plutonium-241, americium-241, uranium-234 and uranium-238. Data from periodic urine assays for plutonium isotopes were used to estimate systemic deposition with a simple equation (Langham et al., 1980). Systemic deposition estimates were computed each time a urine assay was performed, with the most recent computation reflecting the cumulative deposition from all past intakes. Systemic deposition estimates were recorded in the hard-copy health physics files for individual workers. In the late 1980s, a computer database was constructed to list the last reported systemic deposition calculation for plutonium and americium intakes for workers. The electronic database was subsequently lost, but a hard copy of the database was retained. We re-entered these recorded data and included them in our analytic database. We also obtained additional data on systemic deposition estimates from the analytic files of Wilkinson et al. (1987).

Plutonium systemic deposition for plutonium-239 and plutonium-240 was recorded as a percentage of the maximum permissible body burden, based on International Commission on Radiological Protection (ICRP) methodologies. We converted the data for systemic deposition to activities by multiplying the percentages by the maximum permissible bone burden (1,480 Bq) for Pu-239 and plutonium-240, as done by Wilkinson et al. (1987).

Systemic deposition estimates for americium-241 were also made, but are considered to be unreliable because it was learned that radiochemical analyses had been performed with a contaminated tracer. Preliminary analyses indicate that Am deposition estimates correlate with those for plutonium, but it is not yet clear how to best assess this component of internal exposure for epidemiologic analyses that use systemic deposition estimates for exposures to weapons-grade plutonium. The internal dosimetry procedures used in the lung cancer case-control study and described below accounted for all six isotopes in computing internal lung doses.

Job Exposure Matrix for Chemical Exposures

We created a job exposure matrix (JEM) for exposures to toxic chemicals and fibers. Monthly job and building assignments were recorded for 13,480 workers and archived on microfiche records for 1951 to 1989. From microfiche records we abstracted data for job title, organization, and building for each worker for one month (September) a year. We obtained similar data from electronic records from 1986 to 1989. There were a total of 113,777 annual entries for workers between 1951-1989. For each of the 83 buildings, we reviewed historical records on chemicals that were used in all operations to identify documented or suspected carcinogens and substances known to cause acute or chronic health effects.

For the 20 buildings where workers could have been exposed to one or more toxic chemicals, we developed a list of job titles and organization names that were assigned to the workers in the building and conducted in-person interviews with workers who held these jobs in order to document the tasks performed by persons with each job title, the materials used, and to identify jobs with similar exposures.

Information from the interviews was used to develop a written history of all work activities performed within each building. Because production activities changed from time to time over the history of plant operations, the production history of each building was organized into "eras" of similar activities. The interview data described above were used to group organization codes and job titles for each era by similarity of tasks and materials that were handled. With this information, we collapsed 8,740 unique organization codes into 35 general organization codes, and 4,308 unique job titles into 128 general job codes.

Industrial hygienists identified 10 toxic agents that could have posed health risks to workers. They then estimated, for the general organization and general job combinations in each production era, the average annual exposures to each of the 10 agents. These estimates were made for the usual tasks a worker performed. The lowest and highest annual exposures for these job combinations were also estimated. For most chemicals, the estimates were based on published estimates of specific exposure levels reported for production processes similar to those at Rocky Flats. For beryllium exposures, estimates were made with data from a few hundred samples collected with personal air samplers during production era activities. Exposure estimates for all chemicals

were made for concentrations in the breathing zones of workers, accounting for the exposure reduction from respirators, when worn.

We generated annual exposure estimates for each worker by linking in a relational database the database of all production era workers with the data table for general organizations and general jobs and the data table for estimated exposures. Expressing annual exposure as the product of estimated time-weighted average daily air concentration and the hours worked per year maintained consistency between organizations and buildings across time periods. We estimated cumulative exposure by simply adding annual exposures over any time period of interest. We therefore avoided the problems created by making such estimates with qualitative (binary categorical) or semi-quantitative (nominal or ordinal categorical) metrics (Stewart & Herrick, 1991; Armstrong et al., 1992).

The following agents were included in the JEM: asbestos, beryllium, carbon tetrachloride, hexavalent chromium, formaldehyde, lead, methylene chloride, nickel, tetrachloroethylene, and trichloroethylene. For the lung cancer case-control study, exposures to asbestos, beryllium, hexavalent chromium and nickel were analyzed. A cumulative chemical exposure estimate was created for each worker for the four agents by adding annual exposures and adjusting for lag times.

For the years for which individual workers lacked data for exposures to the four agents, estimates were made with the nearby method, as described above. For combinations of buildings, jobs, and organizations for which no exposures were assigned in the JEM, arbitrary exposure estimates were made based on the distributions of exposures assigned to other combinations. A summary of exposures estimated with the JEM has been published by Ruttenber et al. (2001).

Cohort Mortality Data

Vital Status Determination

We defined the production era cohort to include workers in the cohort database who were employed at Rocky Flats for 6 months or more between 1952 and 1989—the period when the plant produced components for nuclear weapons. Subjects in this cohort could have had any job assignment, including clerical work. The production era preceded the era of decommissioning and decontamination, which began January 1, 1990.

For the 9,539 Rocky Flats production workers in the LANL database, vital status was determined through the end of 1993. The names and SSNs for all workers in the production era cohort were submitted to the Social Security Administration for vital status determination through December 31, 1996. This database has uniform reporting for deaths during the mortality follow-up period from the start of 1952 to the end of 1996. Dates of birth and death were obtained from this source for cohort members who had died during this period.

The names and SSNs for the production era cohort were also submitted to the Pension Benefits Information service of Tiburon, CA to identify additional

deceased subjects. This service maintains several databases with death records and pension benefits information for the time period of interest, including the Social Security Administration, Department of Defense, Railroad Retirement Board, Civil Service Commission, and the Departments of Vital Statistics from many states.

Personally identifying information for all workers in the production era database who were not known to be alive were submitted to the National Death Index (NDI) for identification of deaths and coding of multiple causes for deaths that occurred between January 1, 1979 and December 31, 1996. Deaths identified by NDI were returned in electronic format with dates of birth and death, states of death, SSNs, and codes for multiple causes of death classified according to the International Classification of Diseases, 9th revision (ICD-9) (World Health Organization, 1977).

Names and SSNs for all production workers were submitted to the CDPHE to identify subjects who died in Colorado before 1979. For these subjects, we obtained death certificates and had them coded according to ICD-9 criteria for multiple causes by a nosologist. Project staff are continuing to try to identify states of death for subjects who have died before 1979 and are missing death certificates, and to identify persons who died outside Colorado before 1979 who may be missing data for multiple causes of death.

Cancer Incidence Data

The CCCR began collecting data on cancers diagnosed in selected Denver metropolitan hospitals on January 1, 1968. On January 1, 1979, the CCCR achieved complete coverage for the Denver metropolitan area (where most current and former Rocky Flats workers have resided); by January 1, 1988 the CCCR attained coverage for the entire state. The anatomic site, cell type, and behavior of diagnosed cancers were coded according to the International Classification of Diseases for Oncology, Second Revision (Percy et al., 1990).

We compared the personally identifying data in our complete Rocky Flats database with the CCCR database and obtained electronic records for all diagnostic information on cancers reported to the CCCR through December 31, 1996. We reviewed the classification coding to assure compatibility with codes used for background rates from the Surveillance, Epidemiology and End Results (SEER) Registry (Cassinelli et al., 2001).

Between 1999 and 2002, we attempted to determine current addresses for all living former production workers. This work was funded by the U.S. Department of Energy for the purpose of notifying former production workers of past exposures to toxic chemicals and asbestos and to offer them medical screening exams. We used information from first-class mailings, internet directories, and commercial credit data sources to obtain last known address and the last date for which this address was accurate.

We have used the current address data to evaluate the effects of different approaches to right censoring on estimates of standardized incidence ratios (SIRs), calculated in a manner similar to SMRs, using PCLTAS software. A

description of these methods and the estimated of SIRs will be published after peer review.

Lung Cancer Case-Control Study

The main objective of this study was to investigate the association between lung cancer mortality and radiation dose to the lung from internal exposures to radionuclides processed at Rocky Flats, taking into account external radiation dose, exposures to chemical carcinogens, smoking frequency, and other covariates. We used a nested case-control study design that allowed us to examine risk for lung cancer mortality by calculating internal lung doses for 900 individual workers rather than computing these for the entire production era cohort. We realized a similar efficiency in the collection of data on smoking histories.

Selection of Cases and Controls

Cases were drawn from a preliminary database of 22,883 production-era workers according to the following selection criteria: specification of primary lung cancer (ICD-9 code 162) as the underlying or contributing cause of death on the death certificate of a worker who was employed at Rocky Flats for at least 6 months between January 1, 1952 and December 31, 1989.

When the case-control study was initiated, the cohort database was thought to have been complete. After finishing analyses, we discovered the group of 2,448 production-era workers mentioned above. These workers had been monitored for radiation exposure, but were not listed in any of the other databases used to prepare the cohort for selection of cases and controls. It is likely that these workers were employed by subcontractors or by the Department of Energy and its predecessors. Although these subjects were not included in the lung cancer case-control study, they were included in the cohort mortality study.

Because misclassification of primary and metastatic cancers can occur on death certificates, the 193 lung cancer cases were validated with data from the CCCR, when available. We identified 13 of the original lung cancer cases who did not have primary lung cancer. Eliminating these deaths reduced the number of cases from 193 to 180. Twenty-six (14%) of these eligible cases had primary lung cancer listed as a contributing cause on death certificates.

Controls were selected from the same preliminary cohort database from which cases were selected. We used incidence density sampling, which involved selecting controls from the set of subjects at risk (the risk set) at the time of death of each case. Incidence density sampling can be seen as an extension of the person-time approach used in cohort studies (Checkoway, 1989). A case-control study with incidence density sampling uses all available numerator data (cases) and a matched, random sample from the denominator (controls), based on persons at risk at the time subjects became cases.

Because age is a strong risk factor for most cancers, risk sets were defined based on the birth dates (within 2.5 years) of cases. Additional matching criteria included: 1) employment at Rocky Flats for at least 6 months between January 1, 1952 and December 31, 1989; 2) gender; 3) starting work at Rocky Flats at an age younger than the age of the matched case at death; and 4) being alive at the age at death of the matched case.

Case subjects could have been selected as controls in the risk sets of other cases who had died at younger ages. For example, if a cohort member became a case at age 75, he or she was included in the risk sets of cases younger than 75 years if he or she met the other inclusion criteria. Within a risk set, controls were selected without replacement, and a worker could have been selected as a control for more than one risk set. Four controls were randomly selected from each risk set for comparison with each lung cancer case. The number of unique individuals in the risk sets for analyses varied, depending on the characteristics of the cases.

One case was selected as a control three times, one as a control two times, and 12 as controls one time. One control was selected four times; two controls, three times; 56 controls, two times; and 654 controls, one time. A comparison of cumulative internal lung doses (as described below, with no lag period) between these groups of controls showed no large or statistically significant differences (data not shown).

Lung Dose Estimates

Each Rocky Flats worker who was monitored for radiation exposures has a hard-copy health physics file that contains records of bioassays (primarily measurements of plutonium and uranium isotopes in urine) and body, lung and wound counts, as well as reports of accidents or incidents involving radioactive materials. These files are available upon request from the Radiation Protection Division for workers who are currently employed, and from the Federal Records Center for former workers.

Both effective intakes and annual equivalent doses were calculated with the Code for Internal Dosimetry (CINDY), version 1.3C (Streng et al., 1993). The CINDY code is based on the dosimetry model developed by the International Commission for Radiological Protection (ICRP), Publication 30 (ICRP, 1986). The sources of input data for the model were urine bioassay data for plutonium and uranium and lung count data for isotopes of both elements and their decay products.

Each worker's record for accidents and exposure incidents, together with records of periodic analyses of urine for plutonium and uranium isotopes and lung counting were reviewed to first determine an effective intake date based on either the date of a dominant exposure incident, the midpoint of a time period with multiple exposures, or the midpoint between the last date of a urinalysis with no detectable plutonium or uranium and the date of the first positive urine sample, as judged appropriate by the dosimetrists.

Urine bioassay data and lung count data (which were performed starting in 1965), were used in conjunction with the CINDY software to determine the size of effective plutonium intake. Adjustments to the intake date and solubility class for plutonium were made in order to match modeled urine activity with measured activity. The intake of americium-241 was estimated as a ratio of the estimated intake for plutonium-239 and plutonium-241, based on the isotopic ratios in the nuclear materials processed at Rocky Flats.

Equivalent doses for lung and other organs were calculated for each year from first exposure to the end of 1995. Annual internal lung dose estimates were then extracted from CINDY files and included in the exposure database for the case-control study. The database contains a record for each worker for each year of follow-up, with the external penetrating dose, internal lung dose, and chemical exposures for that year.

Dose estimates were made by persons who were supervised by a medical physicist trained by the health physicist who has performed most of the internal dose calculations for Rocky Flats production workers (Daugherty et al., 2001). Persons performing dose calculations were blinded with regard to whether subjects were cases or controls. All dose calculations were reviewed by a medical physicist and a health physicist, who reached consensus on final choices for model parameters.

Smoking Histories

Cigarette smoking frequency was obtained by telephone interviews with surrogate informants (i.e., spouse, next of kin, or former coworker) or from medical records for both cases and controls, regardless of the vital status of the subject at the time of interview. Surrogates were used for collection of data on smoking status of living controls to reduce the bias that could be introduced by the fact that all lung cancer cases were deceased (Gordis, 1982). Although interviewers were blinded to the case or control status of the study subject, this information was sometimes revealed by interviewees in the course of interviews.

Next of kin were identified from the personnel cards and records of benefits recipients at RFETS, telephone directories, death certificates, or a private consumer credit information agency. If no next of kin could be located, former workers who knew study subjects were interviewed. For subjects with no identifiable informant, smoking histories were abstracted from medical records at RFETS, if they were available. Smoking status was included on medical forms filled out by workers during annual physical exams starting in 1978, but was not recorded for all workers.

The goal of the smoking history questionnaire was to first determine smoking status (ever, never) and then to estimate the number of pack-years for study subjects for each year of follow-up. We also asked whether the subject had ever been employed at nuclear facilities other than Rocky Flats. Before conducting the telephone interview, the interviewee was sent an introductory letter explaining the study risks and benefits and policies on data protection and confidentiality. The letter was followed by a telephone call to confirm receipt of

the letter and to schedule a telephone interview. Interviewees were read an informed consent document and asked to provide verbal consent before proceeding with the interview.

STATISTICAL ANALYSES

Cohort Mortality

We used the production era cohort to calculate SMRs for underlying and multiple causes of death. Person-years at risk for an individual worker began on January 1, 1952 for workers hired before this date, or the date of hire for workers hired later, and extended to the date of death or to the end of the period of vital status ascertainment (December 31, 1996). We computed person-years at risk for five-year age and calendar intervals stratified by race (white and non-white) and sex with PCLTAS software for life table analysis (Cassinelli et al., 2001).

The ICD-9 codes for the underlying causes of death for cohort members were grouped into 92 categories. The expected number of deaths for each category were computed by multiplying the number of person-years in each stratum by the age-, race-, sex-, and calendar-year-specific mortality rates for the United States and for the State of Colorado. Standardized mortality ratios were computed with PCLTAS software by dividing observed by expected deaths. Exact 95% confidence intervals were computed when the number of observed deaths was five or fewer, with an approximation suggested by Byar (Rothman & Boice, 1979). SMRs were calculated for both sexes combined and for white males. When a worker's race was not specified in the cohort database, the worker was assumed to be white.

Standardized mortality ratios were calculated in a similar manner for the grouped counts of multiple causes of death. The expected numbers of deaths in each category were estimated with rate files included in the PCLTAS software.

Lung Cancer Case-Control Study

Study Variables

The primary exposure variable was cumulative equivalent dose to the lung (termed cumulative internal lung dose for simplicity) and the outcome was lung cancer mortality. Other exposure variables included cumulative external penetrating radiation dose (termed cumulative penetrating dose for simplicity), cigarette smoking frequency (ever or never, and number of pack-years), cumulative exposure to chemical carcinogens (as determined by the JEM), age at first internal lung dose, calendar period of first hire, and duration of employment. Radiation doses, chemical exposures, and smoking frequency were lagged by 5-, 10-, and 15-year periods before death for cases and before the death of the case with which the control was matched.

The outcome, mortality from lung cancer, was treated as a dichotomous variable in logistic regression models. The independent variables cumulative internal lung dose, cumulative penetrating radiation dose, smoking frequency, age at first internal lung dose, duration of employment, exposures to chemical

carcinogens (asbestos, beryllium, hexavalent chromium, and nickel) were modeled as continuous, dichotomous, interval scale, and design variables (also called dummy variables [Hosmer & Lemeshow, 2000]). All logistic regression analyses included outliers for dose and exposure variables.

Logistic Regression Models

Variables were first analyzed in univariate logistic regression models to test for significant associations with the outcome. With the exception of radiation doses, ranges for each categorical and design variable were specified according to the quartiles for distributions of the data for all subjects. Numerical ranges for categories of radiation exposures were also based on ranges previously reported for epidemiologic studies of nuclear workers. Analyses of age at first internal lung dose were performed with only those subjects for whom unlagged cumulative internal lung doses were greater than zero. Calendar period of first hire was modeled as a design variable.

Confounding by any of the covariates in a model was assessed by including the potentially confounding variable in the model and determining whether it changed, by 10% or greater, the odds ratio that was computed for the main effect in a model without the potential confounder (Mickey and Greenland, 1989).

Variables for the final models were chosen based on either the size of odds ratios and p-values (<0.05), significant contribution to the goodness of fit of the model (as determined by the likelihood ratio test), or for evidence of confounding with cumulative internal lung dose. Internal lung dose was modeled first alone, then with cumulative penetrating radiation dose, smoking in pack-years, chemical exposures (asbestos, beryllium, chromium and nickel), employment duration, period of hire, and age at first internal lung dose added to the model one at a time.

Those variables with statistically significant odds ratios, or those that changed the main effect by more than 10% were retained for the final model. Internal and external radiation doses and chemical exposures were lagged by 5, 10, and 15 years in these explorations. In most all models, the odds ratios for cumulative internal lung dose were highest when the dose was lagged by 10 years. For clarity, data tables are presented for this lag period but not for the others. Because there were only seven female cases, analyses were not stratified by sex.

Data from smoking histories were analyzed with three different approaches. The first maintained matching between cases and controls, thus excluding any matched group of one case and four controls that had one or more subjects who lacked smoking data—leaving 549 subjects for analysis. The second approach used all 730 subjects for whom smoking data were collected by breaking the 1:4 matching and adjusting analyses for birth year in ordinary logistic regression models.

The third approach maintained matching with conditional multiple logistic regression analysis by using a missing-indicator variable to adjust for differences

between those with ($n = 730$) and those without ($n = 170$) smoking histories. This method used data in the incomplete pairs while preserving the matching in the complete pairs; it is regarded as a compromise between matched and unmatched analyses (Huberman and Langholz 1999).

Odds ratios computed for variables of interest with each approach were compared to assess whether the data sets defined by the availability of smoking data were biased samples of the entire group. Logistic regression models were developed with PROC PHREG (Statistical Analysis Software (SAS), 1992). Conditional multiple logistic regression with 1:4 matching was implemented with the discrete logistic model, after forming a stratum for each matched set. Survival time for each control was calculated with the date of death for the matched case.

Cumulative internal lung dose was treated as both continuous and design variables, with study subjects grouped by a variety of dose ranges. Cumulative penetrating radiation dose was modeled as continuous, design, and interval scale variables. Smoking was modeled as dichotomous (ever vs. never), continuous (with units of pack-years) and design variables to assess dose-response relations. Chemical exposure variables were first modeled univariately as continuous and design variables to test for associations with the outcome variable. Age at first internal lung dose was modeled as continuous, categorical, and design variables.

For continuous variables that were converted to design variables, a variety of cut points were explored to determine whether arbitrary choices biased odds ratios. We did not detect such an effect for any of the variables we examined. The final cut points reflect either quantile distributions for variables, or categories that have been reported in previous studies.

Interactions were assessed between cumulative internal lung dose and the following covariates: smoking, cumulative penetrating radiation dose, age at first internal lung dose, and cumulative exposures for each of the four chemicals. Interaction terms composed of both continuous and design variables were first modeled as main effects and then with potentially confounding variables.

To test for linear trends of odds ratios with cumulative internal lung dose, we categorized doses into four and six groups and coded these groups numerically from one to four and one to six. We then included these categorical variables in logistic regression models and tested for trends in odds ratios with the chi square statistic. To evaluate the effect of the highest dose category on a trend, we switched the codes for the low and medium dose groups and re-ran the logistic regression analyses. If the trend remained positive and statistically significant after this manipulation, then we concluded that the trend was substantially influenced by the odds ratio for the highest dose category.

Statistical Power

Statistical power and sample size analyses were performed for the cumulative internal lung dose and cumulative penetrating radiation dose distributions used in the final logistic regression models. The power analyses for

cumulative internal lung dose controlled for age and cumulative penetrating radiation dose and the power analyses for cumulative penetrating radiation dose controlled for age and internal lung dose. The age variable was categorized into ten similar-sized age groups according to the distribution of the data. These analyses indicated that, with 1:4 matching, this study had 81% power to detect an odds ratio of 2.0 or greater for cumulative internal lung dose divided into three levels and modeled as design variables. There was 55% power to detect an odds ratio of 2.0 or greater for three categories of cumulative penetrating radiation dose modeled as design variables.

RESULTS

Cohort Mortality

We identified 25,661 current and past employees of DOE and its contractors who worked at the plant between January 1, 1949 (the first year of hire indicated in the production era database) and July 30, 1994 (the cut-off date for obtaining data on Rocky Flats workers). Of this group, 763 were missing dates of hire. There were 19,059 workers hired between January 1, 1949 and December 31, 1989—the date on which production activities were stopped at Rocky Flats. This group is slightly larger than the one reported by Ruttenger et al. (2001) due to the correction of hire and termination data and other editing improvements in the cohort database subsequent to the publication of this article.

For epidemiologic analyses, we restricted our study to a production era cohort comprising workers who were employed for six months or more—reducing the number of eligible subjects to 16,518. Of this group, 117 had invalid SSNs, 64 subjects were missing dates of birth and 4 had coded death certificates, but no dates of death. To date, we have been unable to obtain death certificates for 30 deceased workers. After excluding subjects with these missing data, the production era cohort used for SMR analyses comprised 16,303 production workers.

There were 362,617 person-years at risk for SMR analyses (Table 1). Production workers were predominantly non-Hispanic males born after 1930 and hired after 1968. About 40% of the cohort were employed at the site after production work ceased. Over 75% of deaths occurred after 1980; at the end of the follow-up period, 87% of workers were still alive.

Compared with national mortality rates, all Rocky Flats production workers had significantly lower SMRs for all underlying causes of death, all cancers, cardiovascular diseases, accidents, and homicides (Table 2). The SMRs were elevated for cancers of the stomach, rectum, brain and other central nervous system sites, connective and other soft tissue, as well as for unspecified neoplasms of the nervous system. The SMR for other and unspecified anemias was also elevated. Based on 95% confidence intervals, none of the elevated SMRs was statistically significant.

When SMRs for all production workers were computed with Colorado mortality rates, small increases over the SMRs computed with national mortality rates were noted for most cancers (Table 3). The SMR for unspecified nervous

system neoplasms was, however, statistically significant. Standardized mortality ratios for white males were similar to those for all cohort members, with the exception of higher SMRs for other and unspecified anemias (Tables 4-5).

The ten deaths with diagnoses of nervous system neoplasms of unspecified morphology and behavior comprised eight neoplasms of the brain (ICD-9 code 239.6), and three neoplasms of an endocrine gland or other part of the nervous system (ICD-9 code 239.7)—two listed as contributing causes and one as an underlying cause. Seven of the eight brain neoplasms listed as underlying causes were the ones reported by Wilkinson et al. (1987), and one occurred after the end of their follow-up period.

Malignancies of the brain and other central nervous system sites comprised 29 diagnoses of unspecified malignancies of the brain (ICD-9 code 191.9)—with one listed as a contributing cause—and one each of a malignancy of the spinal cord (ICD-9 code 192.2), the brain stem (ICD-9 code 191.7) and the temporal lobe (ICD-9 code 191.2), listed as underlying causes.

The underlying causes of death for other and unspecified anemias included five diagnoses of aplastic anemia (four with ICD-9 code of 284.9 and one with ICD-9 code of 284.0) and one diagnosis of an unspecified anemia (ICD-9 code 285.9). All 8 connective and other soft tissue cancers were categorized as site unspecified (ICD-9 code 171.9).

The SMRs computed for multiple causes of death for all cohort members with United States mortality rates were similar to those for underlying causes of death and are not reported. Diagnoses listed as contributing causes of death on death certificates (such as cancers of the digestive and lymphatic and hematopoietic systems will improve statistical power in analyses of exposure-disease relations within the cohort (Table 6). Asbestosis (ICD-9 code 501) was listed as the underlying cause of death for three subjects and as a contributing cause for one subject. Pneumoconiosis (ICD-9 code 503) was the underlying cause for one death, and the contributing cause for another.

Preliminary Cancer Incidence Data

We identified 1,259 production workers who had cancers diagnosed and reported to the CCCR. Compared with cancer mortality data, there are substantial additions of subjects for all cancers, and for subjects with cancers of the intestine, rectum, female breast, prostate, bladder, skin, and thyroid (Table 6). Data for cancer incidence indicate that improvements in statistical power may outweigh the loss of person-years from left and right censoring for leukemias (n=49), other lymphatic and hematopoietic malignancies (n=51), as well as for breast cancer in females (n=76).

Lung Cancer Case-Control Study

Descriptive Statistics

All 900 subjects were included in univariate analyses with ordinary logistic regression and in matched analyses that assessed smoking frequency using a missing indicator variable (Table 7). We included 730 subjects in the unmatched

analyses for all subjects who had smoking frequency as a covariate, and 549 subjects in the matched analyses for case-control pairs with smoking data.

By definition, all case subjects were deceased; only 30% of controls had died by the end of the follow-up period (Table 7). Control subjects were distributed evenly over the four periods of hire, but cases were more likely to have been hired between 1960 and 1967 than in other periods. For the three different subject groups, controls were employed from one to two years longer than cases. The mean age for first internal lung dose was from one to three years greater for cases than for controls. At death, controls were, on average, nine years younger than cases (Table 7).

Ninety-eight percent of the total internal lung dose for cases (the sum of cumulative internal lung doses for individual case subjects) was from the combination of plutonium isotopes and americium-241. For cases, internal lung doses from uranium-234 and uranium-238 accounted for 2.2% and 0.06% of this total dose, respectively. Twenty cases received contributions to internal lung doses from uranium-234 and seven received contributions from uranium-238.

Ninety-six percent of the total internal lung dose for control subjects was from a combination of plutonium isotopes and americium-241; uranium-234 and uranium-238 accounted for 4.3% and 0.004% of this total dose, respectively. Fifty controls received contributions to internal lung doses from uranium-234, and three from uranium-238.

Among workers with internal exposures to uranium-234, lung doses ranged from 1 to 12,303 mSv and 96% had doses lower than 400 mSv. Among workers with internal lung exposures from uranium-238, lung doses ranged from 1 to 23 mSv.

For both cases and controls, median cumulative internal lung doses were zero and the means were close to the 75th percentiles (Figure 1). Cases had a lower mean dose than controls. Similar percentages of cases (52.2%) and controls (51.2%) received cumulative internal lung doses that were greater than zero (data not shown).

Subjects in the case-control study had higher mean cumulative doses from penetrating radiation than all subjects in the production era cohort (data not shown). Median, 90th, and 95th percentiles for cumulative external penetrating radiation doses—both un-lagged and lagged by 10 years (Figure 2)—were slightly higher for cases than for controls.

For subjects hired between 1951 and 1959, median cumulative internal lung doses (lagged by ten years) were higher for controls than for cases; for workers hired between 1960 and 1989, cases had higher median and mean cumulative internal lung doses than controls (data not shown). There appears to be a trend of increasing cumulative internal lung dose with increasing employment duration that is more pronounced for cases than for controls for subjects employed for 20 years or fewer (Figures 3 and 4). Only one case (0.5%) worked for more than 29 years, while 45 controls (6.3%) worked for 30 years or more.

For cases, the workers with the highest cumulative doses received their first dose between the ages of 35 and 60, while controls with the highest cumulative doses received their first dose between the ages of 25 and 60 (Figures 5 and 6). Only 3 cases (3.1%) received their first dose before age 35, while 44 controls (10.7%) received their first dose before age 35.

Analyses with Ordinary Logistic Regression Models

In a univariate model, the odds ratio for cumulative internal lung dose, modeled as a continuous variable, was not elevated (Table 8). Cumulative internal lung dose, modeled as a dichotomous variable, produced an odds ratio that was elevated, but not statistically significant. When cumulative internal lung dose was categorized into four groups and analyzed as a continuous categorical variable, the odds ratio for the highest category was elevated, but not significantly. Cumulative internal lung dose, modeled as design variables with two different stratifications of dose, produced odds ratios that were increased for dose categories >400 mSv, but not for the group >940 mSv; neither odds ratio was statistically significant.

Odds ratios were not elevated when cumulative penetrating radiation dose was modeled as a continuous, dichotomous, continuous categorical (data not shown) or design variable (Table 9). Calendar period of first hire was significantly associated with lung cancer in the univariate analysis, with the highest risk observed for subjects hired between 1960 and 1967 (Table 9). The odds ratio for age at first internal lung dose, modeled as a continuous variable, was of borderline significance in the univariate analysis (Table 9).

Smoking frequency was modeled as continuous, dichotomous, categorical and design variables. According to likelihood ratio test, the best model included smoking as a design variable. In a univariate model, each of the four smoking frequency categories showed significantly elevated risks.

Length of employment, modeled as a continuous variable (the best model based on a comparison between the likelihood ratio tests for this variable, categorical, and design variables) was significantly and negatively associated with lung cancer (Table 9).

Odds ratios for cumulative internal lung dose design variables were not elevated for workers employed 10 years or fewer were not elevated (Table 10). For workers employed for 5 to 14 years, the odds ratios for these design variables increased with increasing dose, but were not statistically significant in any of the dose strata. The odds ratios for the highest cumulative internal lung dose category in the employment duration categories of 10-20 years and 15-25 years were significantly elevated, and the odds ratios increased with dose for the workers employed for 15-25 years.

Only the highest dose category had an elevated odds ratio for workers employed 20 to 30 years. The odds ratios for all cumulative internal lung dose categories were significantly less than 1.0 for workers employed more than 25 years. In a multiple logistic regression model for workers employed for 15 to 25 years, odds ratios for the six cumulative internal lung dose groups increased with

increasing dose over all six groups, and the odds ratio for the highest dose category was significantly elevated (Table 11). A test for trend using these six dose categories and controlling for period of hire and employment duration was statistically significant.

Univariate odds ratios were calculated for cumulative internal lung dose for several calendar periods of first hire (Table 12). Significantly elevated odds ratios were observed for the highest cumulative internal lung dose categories for the two groups of workers hired between 1960 and 1975.

The largest percentages of cases and controls received their highest single internal lung doses in 1970 (data not shown). According to health physicists at RFETS, doses received in 1970 were primarily from exposures resulting from the 1969 fire and clean-up operations that followed. Of the 30 subjects who received their highest doses in 1970, 12 (40%) were cases. In a univariate logistic regression model, the odds ratios for having received the highest dose at this time were 3.68 (95% CI 1.62, 8.38), 3.57 (95% CI 1.42, 8.93), and 4.09 (95% CI 1.48, 11.35) for 5, 10 and 15 year lag periods, respectively (data not shown).

About 90% of cases and controls had no routine exposure to asbestos or beryllium, and about 80% of cases and controls had no routine exposure to hexavalent chromium or nickel. None of these four chemical carcinogens were significantly associated with lung cancer in univariate logistic regression analyses (data not shown).

Conditional Multiple Logistic Regression Models: Case-Control Pairs with Smoking Data

In conditional multiple logistic regression analyses with the case-control pairs that had data on smoking frequency (as described in Table 13), odds ratios were elevated for cumulative internal lung doses greater than 100 mSv when lagged by 5-, 10-, and 15-year periods, and were of borderline statistical significance for 5- and 10-year lag periods, but not for the 15-year period.

Cigarette smoking was strongly associated with lung cancer mortality for all pack-year levels at each lag period for radiation doses and smoking frequency. The strongest associations were with the highest pack-years category for each lag period. The odds ratios for employment duration, modeled as a continuous variable, were significantly less than 1.0 for all three lag periods.

Two interaction terms were added to the model described in Table 13. The odds ratio for the interaction between the highest cumulative internal lung dose group and the highest cumulative penetrating radiation dose group was elevated, but not statistically significant when both dose variables were lagged by 10 years (OR=1.20, 95% CI 0.26, 5.44). The interaction term with smoking frequency as a continuous variable and the highest dose group for cumulative internal lung dose (lagged by 10 years) was slightly elevated and of borderline statistical significance (OR=1.01, 95% CI 0.99-1.03).

In an unmatched analysis limited to subjects with above-zero cumulative internal lung doses and smoking histories, age at first plutonium dose was

significantly associated with the outcome with a lag period of 10 years for radiation doses and smoking frequency (Table 14). Adjusting for age at first lung dose produced slightly higher odds ratios for cumulative internal lung dose than the unadjusted ones, but none were statistically significant. The odds ratios for cumulative penetrating radiation dose were also elevated, but were not statistically significant.

Multiple Logistic Regression Models:
Unmatched Subjects with Smoking Data

The matching of cases and controls was broken and the data for all subjects who had smoking histories were analyzed with ordinary multiple logistic regression models, adjusting for birth year. For each of the three lag periods for radiation doses and smoking frequency, odds ratios for internal lung dose categories above 100 mSv were elevated, but were only statistically significant for cumulative lung doses above 400 mSv for doses lagged by 5 and 10 years (as illustrated in Table 15).

Odds ratios for cumulative penetrating radiation dose were not significantly elevated for any group or lag period in models with all subjects. Odds ratios for smoking frequency were significantly elevated for all categories of pack-years at all lag periods. The odds ratios for employment duration were significantly lower than 1.0 for models with 5- and 10-year lag periods.

We evaluated interactions between selected variables in models with the variables described in Table 15. An interaction term for cumulative internal lung dose and smoking frequency, both modeled as continuous variables, was not statistically significant for any of the lag periods (data not shown). An interaction term for cumulative internal lung dose greater than 400 mSv and smoking frequency modeled as a continuous variable was elevated for each of the three lag periods (as described in Table 15), but was of borderline statistical significance.

The odds ratios for the interaction terms for cumulative internal lung dose and cumulative penetrating dose treated as continuous and design variables were not significantly elevated at any lag period for either dose measured continuously or for any dose level for design variables (data not shown).

In analyses limited to subjects with above-zero cumulative internal lung doses, odds ratios for age at first internal lung dose were elevated and of borderline statistical significance for all lag periods (as described in Table 16). Compared with the model in Table 15, adjusting for age at first lung dose produced higher odds ratios for cumulative internal lung dose and cumulative penetrating radiation dose categories, but none were statistically significant.

Conditional Multiple Logistic Regression Models:
All Subjects with Analysis of Smoking Frequency

In conditional multiple logistic regression models for all cases and controls with a missing indicator variable to adjust for missing smoking data, the odds ratios for cumulative internal lung doses for above-zero lung dose categories

were elevated for all radiation dose and smoking frequency lag periods (as illustrated in Table 17). Only the odds ratios for cumulative internal lung doses greater than 400 mSv were significantly elevated in models with 5- and 10-year lag periods (as illustrated in Table 17).

Cumulative penetrating radiation dose was not significantly associated with lung cancer at any dose level or for any lag period for models with all subjects (as described in Table 17). Odds ratios for smoking frequency, modeled as a design variable, were significantly elevated for every frequency category for each lag period, and increased with increased smoking frequency.

Odds ratios for employment duration were significantly less than 1.0 for each lag period (Table 17). The interaction term for cumulative internal lung doses greater than 400 mSv and smoking frequency modeled as a continuous variable was elevated and of borderline statistical significance for each of the three lag periods (data not shown).

In analyses restricted to subjects with above-zero cumulative internal lung doses, the odds ratio for age at first internal lung dose was significantly elevated for a 10-year lag period (Table 18), and of borderline significance for 5- and 15-year lag periods (data not shown). The odds ratios for cumulative penetrating radiation dose were also elevated in this model, but were not statistically significant. The odds ratio for the interaction term with the highest cumulative internal lung dose category and pack-years of smoking as a continuous variable was only slightly elevated and of borderline statistical significance (data not shown).

Conditional multiple logistic Regression Models:

All Subjects, Excluding Smoking Frequency

Conditional multiple logistic regression models were constructed with data for all subjects, excluding the variables for smoking frequency. In these models, odds ratios were significantly elevated for cumulative internal lung doses greater than 400 mSv, lagged by 10 years (Table 19), and elevated with borderline significance at 5- and 15-year lag periods. For each of the three lag periods, odds ratios for cumulative internal lung dose increased as dose categories increased and there was a statistically significant linear trend for the model with doses lagged by 10 years (Table 19).

The odds ratios for duration of employment were significantly less than 1.0 for all lag periods. Workers hired between 1960 and 1967 had significantly elevated odds ratios for all three lag periods. The odds ratios for cumulative penetrating radiation were not significantly elevated for any dose category for any lag period.

Cumulative internal lung doses were stratified into six categories in a conditional multiple logistic regression model that adjusted for cumulative penetrating radiation dose, period of hire, and employment duration, with radiation doses lagged by 10 years (Table 20). The odds ratio was highest and significantly elevated for the category for cumulative internal lung doses that ranged from greater than 400 mSv to 940 mSv. Compared with this category,

the odds ratios for the two higher dose categories were lower and not statistically significant.

For the subjects with above-zero cumulative internal lung doses with a 10-year lag period, the odds ratio for age at first internal lung dose was significantly elevated (Table 21), and elevated with borderline significance for 5- and 15-year lag periods. The odds ratios for cumulative penetrating radiation dose were also elevated, but were not statistically significant. Restricting analyses to subjects with internal radiation exposures did not change the dose-response relation noted in Table 20 when cumulative internal lung dose was stratified into 6 design variables (data not shown).

Since models with lung doses grouped as six design variables did not show increases in odds ratios over the two highest categories, we explored the possibility that the internal dosimetry model produced inaccurate estimates for these categories. We examined whether adjusting models for certain covariates of lung dose such as the year of first positive lung dose, the number of years with a positive lung dose, and the average rate of decline in annual lung dose from the year of highest dose would explain our unique findings.

We found that adjusting for the number of years a subject received an internal lung dose (modeled as a continuous variable with doses lagged by 10 years) produced much higher estimates of odds ratios for all dose categories, but did not alter appreciably the dose-response relation (Table 22). Moreover, there was a significant inverse relation between the number of years with a positive lung dose and the risk for lung cancer. This relationship is what would be expected if the dose estimates for controls had been overestimated due to long duration periods as compared with those for cases. These results suggest that the CINDY code overestimates doses delivered to the pulmonary epithelium over long time intervals.

Other Analyses

Age at first internal lung dose and attained age (age at end of study period or age at death), were also evaluated for interaction with cumulative internal lung dose. The age variables were modeled as continuous variables and cumulative internal lung dose as both continuous and categorical variables. None of the odds ratios for the interaction terms were statistically significant (data not shown).

The previously described analyses of the risk for age at first internal lung dose were restricted to subjects with above-zero cumulative doses. We explored the effect of the age at which internal lung doses were received on the risk for lung cancer in models that included all subjects by creating a series of variables that recorded the cumulative internal lung doses received by ages 40, 50, and 60 and stratified these by the four dose categories (as design variables) used in previous analyses. Three conditional multiple logistic regression models were constructed, one with each of the sets of design variables for doses received by ages 40, 50, and 60. All analyses produced odds ratios similar to those estimated for all subjects in the model that was not adjusted for age at first dose (data not shown). In these models, there was no evidence of increased risk from

higher cumulative doses at older ages, as compared with younger ages. The odds ratios for cumulative penetrating radiation dose were also not elevated in these models.

These analyses suggest that both the effects of age at first internal lung dose and the risk for cumulative penetrating radiation dose are confined to those subjects who actually received internal lung doses as opposed to subjects who may or may not have received internal doses.

In all analyses with penetrating radiation doses, missing doses were imputed using the nearby method (Ruttenber et al., 2001). An alternative to the nearby method is to assign zeros for all missing doses. We compared these two methods in the conditional multiple regression model for all subjects without smoking data, as described in Table 19, and found no difference in odds ratios computed with the two different methods for treating missing external penetrating doses.

Cumulative exposures to four carcinogens—*asbestos, beryllium, hexavalent chromium, and nickel* (lagged by 5, 10, and 15 years) were not associated with lung cancer mortality when modeled separately and with conditional multiple logistic regression models that included previously reported categories of cumulative internal lung and penetrating radiation doses without smoking frequency variables (data not shown).

Interaction terms for cumulative internal lung dose and cumulative penetrating radiation dose (both lagged by 10 years) were not statistically significant in models without smoking frequency with four dose categories for cumulative internal lung dose and three for cumulative penetrating doses.

We also explored relations between plutonium exposure and lung cancer with plutonium systemic deposition estimates. Of 900 study subjects, 49% (n=439) had systemic deposition data available. Thirty-three percent (n=293) of the 900 workers from this study had systemic deposition estimates greater than zero, compared with almost 60% of cumulative internal lung doses that were greater than zero.

Odds ratios for systemic deposition were not significantly elevated when expressed as a dichotomous variable (zero vs. above-zero) in a conditional multiple logistic regression model without smoking data—both in a univariate model and in a model that adjusted for employment duration, year of hire, and cumulative penetrating radiation dose.

When systemic deposition estimates were divided by quartile distributions and modeled as design variables in the previously described model, the odds ratio for the highest systemic deposition group was 1.23, but was not statistically significant (data not shown). A test for linear trend (as described below) over the four categories for systemic deposition was not statistically significant.

In the interviews for smoking histories, respondents for 61 of 730 subjects indicated that the subject had worked at another nuclear weapons or nuclear power facility. Several of the subjects reportedly worked at other nuclear weapons facilities—including Los Alamos, Hanford, and Oak Ridge—some for as long as 20 years. The influence of a categorical variable for this additional

source of radiation exposure was examined in all models and found not to be statistically significant (data not shown).

Bias and Confounding with Smoking Data

We were unable to obtain data on smoking frequency for 31.7% of cases and 15.7% of controls. For all lag periods, mean cumulative internal lung dose and mean cumulative penetrating radiation dose were similar between the cases and controls with data on smoking frequency. For all lag periods, both cases and controls without smoking data had mean cumulative penetrating and internal lung doses that were substantially lower than subjects for whom smoking data were available.

Excluding subjects for lack of smoking data, therefore, excluded proportionately more cases than controls with low cumulative penetrating and internal lung doses. Such removal would be expected to produce a biased increase in the odds ratios for lung cancer mortality. This bias is illustrated by the increased odds ratios for cumulative penetrating dose in analyses restricted to case-control pairs with smoking data, as compared with the odds ratios for analyses with all subjects (Table 23). In contrast to the lowering of odds ratios for cumulative penetrating dose with the inclusion of cases and controls without smoking data, the odds ratios for cumulative internal lung doses remained about the same in models with all subjects (Table 23).

The impact of selection bias on the risk for calendar period of first hire is greater from limiting selection to subjects with above-zero cumulative internal lung doses than from limiting selection to those with availability of smoking data (Table 23).

To assess confounding between smoking frequency and cumulative internal lung dose, each of the three study populations defined by availability of smoking data were modeled both with and without the variable for smoking frequency (Table 24). Including smoking frequency as a design variable did not significantly change the association between cumulative internal lung dose and lung cancer in any of the models—indicating that smoking frequency does not confound the relation between cumulative internal radiation dose and risk for lung cancer mortality.

Because of the selection bias introduced by removing subjects without data for smoking frequency and because smoking appears not to confound the relationship between cumulative internal lung dose and lung cancer mortality, we think the best model for estimating risks for lung cancer from internal and external radiation doses is a matched analyses for all subjects, without smoking data (as described in Tables 19-22).

DISCUSSION

Cohort Mortality

Standardized mortality ratios for all causes of death and all cancers are significantly lower than one. Our SMR estimates are similar to those for the previous study of Rocky Flats workers (Wilkinson et al., 1987) and for Los

Alamos workers (Wiggs et al., 1994). Because we used 95% confidence intervals with prior hypotheses for only elevated risks for workplace exposures, SMRs of borderline statistical significance should not be disregarded. The low SMRs for all causes reflect a strong healthy worker effect—another reason for studying further cancer sites with SMRs that are elevated but not statistically significant.

We found non-significantly elevated SMRs for cancers of the stomach and rectum. The previous study of plutonium-exposed Rocky Flats workers (Wilkinson et al., 1987) did not detect elevated SMRs for these cancers, but did report a non-significant increase in the rate ratio for esophageal, stomach, and colon cancer for plutonium-exposed production workers, as compared with workers with little or no plutonium exposure. Wiggs et al. (1994) noted a non-significant increase in relative risk for cancer of the rectum for plutonium-exposed workers as compared with workers with little or no exposure.

Reyes et al. (1984) first identified elevations in brain neoplasms for plutonium workers. Wilkinson et al. (1987) found a statistically significant elevation in the SMR for unspecified brain neoplasms, based on 7 cases. They also found a non-significantly elevated SMR for brain cancer and an elevated rate ratio for unspecified brain tumors in workers with a cumulative external penetrating radiation doses greater than 0.01 Sv, as compared with those who had lower doses. The rate ratio for brain cancer was not elevated in a similar comparison.

Our findings indicate that the elevated SMR for unspecified neoplasms of the brain has persisted and remained statistically significant. We provide additional evidence with an elevated SMR for cancers brain that is of borderline statistical significance. It appears the sizable increase in brain cancers noted in our study over the six subjects reported by Wilkinson et al. (1987) reflects recent improvements in diagnostic methods for brain cancer.

These findings are consistent with a statistically significant dose-response relation between cumulative external radiation dose and cancers of the brain in Los Alamos workers (Wiggs et al., 1994). Omar et al. (1999) also noted a statistically significant dose-response relation for brain cancer incidence and cumulative external radiation dose for all radiation workers at Sellafield, and SMRs for brain cancers have been elevated in other cohorts of nuclear workers (Alexander, 1991).

The SMRs for cancers of connective and other soft tissue were elevated for each of the four analyses we performed. These findings are consistent with those reported from a cohort study of Mayak workers (Koshurnikova et al. (2000). Such findings are biologically plausible in that connective tissue cancers occur adjacent to bone—though the location of a tumor is not specified on death certificates. Bone cancer was identified as the underlying cause of death for one worker and listed as a contributing cause for another. These results suggest the need for further study of bone and connective tissue cancers with improved external and internal dosimetry, and with more detailed diagnostic data from the CCCR.

We detected elevated SMRs for anemias, with four of the five deaths attributed to aplastic anemia. Bone marrow hypoplasia and deaths from aplastic anemia were noted for Mayak workers employed during early operational years when penetrating and internal doses were substantially higher than those received by Rocky Flats workers (Okladnikova et al., 1994). To our knowledge, other studies of radiation workers have not reported increases in mortality from aplastic anemia.

The lung cancer SMRs computed with United States and Colorado mortality rates are significantly less than one. These findings are substantially different from the elevated SMRs identified for sub-cohorts restricted to plutonium-exposed workers at Los Alamos (Wiggs et al., 1994) and Mayak (Koshurnikova et al., 1996). They also contrast with the results from our case-control study, and the dose-response relations determined for Mayak workers (Khokariakov et al., 1996; Tokarskaya et al., 1997). Our lung cancer SMRs are, however, slightly higher than those estimated for the entire Los Alamos cohort (Wiggs et al., 1994).

Preliminary Cancer Incidence Data

The cancer incidence data collected through 1996 provide additional cases of cancer for more detailed analyses with cohort and case-control studies. For deaths with cancer recorded as the underlying cause from 1952 through 1996, 5% occurred between 1952 and the end of 1967—the period for which there was no coverage by the CCCR; 16% occurred between 1968 and the end of 1978, when there was incomplete coverage for metropolitan Denver counties; 29% occurred between 1979 and the end of 1987, when there was complete coverage for Denver metropolitan counties, but incomplete coverage for the entire state; and 50% occurred in 1988 or later, when there was complete coverage for the entire state.

Because 97% of the cohort was still alive in 1979, the cancer incidence data will, over time, become a reliable source of data for studies of cancer in the Rocky Flats workforce, as long as the addresses of cohort members are checked periodically to identify those who have moved from Colorado.

We have recently completed address searches for the production era cohort and these data will help maximize the number of person-years that can be included in cohort-based analyses. We have also completed an assessment of the effects on incidence rates of different criteria for left and right censoring, standardized incidence ratios, and statistical power. Based on these findings, we have estimated standardized incidence ratios for males in the production era cohort and will report these findings after peer review.

Lung Cancer Case Control Study

Both univariate and multiple variable models identified associations between cumulative internal lung dose and lung cancer mortality. The risk for lung cancer from internal lung dose was confounded by cumulative penetrating dose, duration of employment, and calendar period of hire, but not by smoking

frequency. In some models there was a small interaction between smoking frequency and the highest of four cumulative internal lung dose categories, but the interactions were of borderline statistical significance. The combined effect of these two lung carcinogens deserves further study.

In multiple logistic regression models both adjusted and not adjusted for smoking frequency, there were statistically significant risks for lung cancer mortality at cumulative internal lung doses above 400 mSv, when they were lagged by 5- and 10-year periods. There was also a linear trend in odds ratios when these doses were divided into four categories. When doses were grouped into six design variables, the dose-response trend was not stable for doses above 644 mSv.

It is not clear why odds ratios for cumulative internal lung dose did not increase across the high dose categories for analyses of all subjects. We think that one or more of the following explanations are likely: 1) a strong healthy-worker survivor effect (Baillargeon & Wilkinson, 1999) that may have been influenced by routine health screening; 2) errors in internal dosimetry associated with different chemical forms of plutonium isotopes; 3) errors in internal dosimetry with regard to estimating the effects of chelation therapy; 4) errors in the ICRP-30 lung model with regard to estimating dose to the pulmonary epithelium over long time periods; 5) selection bias produced by matching controls with internal doses with cases that may never have been at risk for internal exposures.

Studies of Mayak workers have demonstrated elevated lung cancer risk for plutonium-exposed workers. In one study of Mayak workers, mean "lung-absorbed doses" were 0.94 Gy for cases and 0.3 Gy for controls (Tokarskaya et al., 1995)-- which translate roughly to 18,800 mSv and 6,000 mSv for cases and controls, respectively. By comparison, mean cumulative internal lung doses for Rocky Flats workers in our study were 210 mSv and 388 mSv for cases and controls, respectively. Our case-control analyses indicate, therefore, that the risk for lung cancer originally identified for Mayak workers extends to the lower doses received by workers in U.S. weapons facilities.

Age at first internal lung dose was a significant risk factor in models with subjects who received internal doses. The effect of age at radiation exposure upon cancer risk has been identified for doses of penetrating radiation (Stewart and Kneale, 1996; Gilbert et al., 1993; Vorobtsova et al, 2000; Tubiana, 1999). Our alternate analyses with all subjects did not show a risk for age at which cumulative internal lung doses were received. There may be a difference between the effect of age at first dose and the ages at which doses were received. It is also possible that the effect of age at first dose is an artefact of selection bias or due to some other factor. Cohort-based analyses with estimates for annual internal lung doses would clarify this issue.

The odds ratios for lung cancer mortality from smoking ranged from 2.05 to 7.94, depending on the model and the categories chosen for pack-years. Tokarskaya et al.(1995)—in the only other plutonium worker study that included smoking histories in analyses—reported an odds ratio of 6.6 for Mayak workers who ever smoked, compared with those who never smoked. Gilbert et al.(1990)

reported the results of a case-cohort analysis of lung cancer, cumulative penetrating radiation, and smoking among 531 males at the Hanford site. Relative risks in this study ranged from 3.8 (95% CI 1.2, 12.0) for former smokers to 24.1 (95% CI 8.6, 68.0) for current smokers who smoked two packs or more per day.

Analyses of lung cancer risks with a case-control design and data for plutonium systemic deposition showed no relation between this measurement and lung cancer mortality. Ruttenber et al. (2001) reported a range of three orders of magnitude in lung dose for estimates of plutonium systemic deposition below about 50 Bq, indicating the high potential for misclassification of dose. Using dosimetry models to estimate cumulative internal lung doses permitted the detection of risks for lung cancer. It is likely that misclassification of dose is responsible for not detecting risks for lung cancer in studies of plutonium workers at Rocky Flats and Los Alamos.

In preliminary cohort-based analyses, we have detected increased risks for plutonium exposure using the systemic deposition variable. These results suggest that future cohort-based studies with improved internal dose estimates will yield estimates of excess risk per unit dose.

Confounding by Length of Employment and Period of Hire

In the multiple logistic regression models, there is a statistically significant, inverse relationship between length of employment and lung cancer risk. In univariate models, the odds ratios for most above-zero cumulative internal lung dose categories (lagged by 10 years) were less than one for workers employed for 10 years or fewer, or for more than 20 years (Table 10). For workers employed for 10 to 25 years, odds ratios increased with cumulative internal lung dose when doses were grouped by both four and six design variables (Table 10).

In multiple logistic regression models, workers first hired before 1968 were at increased risk for lung cancer compared with workers first hired in 1968 or later. The risk was highest for those first hired between 1960 and 1967, when 36% of cases were hired. Risks associated with year of first hire were noted in univariate analyses, and actually increased after adjusting for cumulative internal lung dose.

There is not an obvious explanation for confounding by length of employment and period of first hire. Internal dosimetry models supposedly account for the accumulation over time of doses to the organ at risk, and if accurate, should not be influenced by duration of employment or period of first hire.

This relationship may be explained by healthier workers being employed for longer time periods than those who were less healthy. Controls, on average, lived longer and worked longer than cases. A similar decrease in risk was noted among Hanford workers employed more than 30 years (Baillargeon and Wilkinson, 1999). The relation between healthy workers and decreased risk may help explain the confounding by length of employment, but appears not to explain why risks are high for workers first hired before 1968 as compared with those

who were hired later, and why the risks are highest for workers first hired between 1960 and 1967.

The elevated risk for workers who received their highest annual dose in 1970—the year after many workers received internal exposures from a serious fire and the subsequent clean-up activities—suggests that dose estimates for these exposures may be inaccurate. The particle sizes or solubilities of plutonium compounds produced in the fire may have been different than those produced during usual production processes.

It is possible that workers who were involved in accidents or other high dose incidents may have decided to leave the Rocky Flats workforce sooner than others. High inhalation exposures to plutonium occurred during the 1957 and 1969 fires, possibly explaining the risks for periods of first hire and length of employment. This explanation would not, however, explain why dose-response relations are different for other periods of first hire or employment durations.

For length of employment and period of first hire to confound the relationship between dose and risk for lung cancer, each variable must affect both dose and lung cancer risk. Though duration and time period of employment may certainly affect the probability of an exposure and subsequent dose, they should not affect the estimation of the size of the dose or dose-response relationships. A worker employed for 10 years who received a high dose and survived for 20 years should have the same cumulative lung dose as a worker with the same dose and survival period, but who was employed for 20 years—if the dosimetry is accurate. The same should be true for workers with different periods of hire.

It appears that the most logical way for length of employment and period of first hire to operate as confounders is by affecting errors in dose estimation. There are two and perhaps more ways this could have occurred. If the actual dose delivered to the pulmonary epithelium changes over time but the estimated cumulative dose does not—by sequestration of plutonium in the lymphatics, for instance—then the actual lung cancer risk for high doses would be lower for persons whose cumulative lung dose accrued over long time periods as compared with short time periods.

For example, two workers with 100 mSv cumulative internal doses to the lung—one with the dose integrated over 5 years, the other over 20 years, may not have the same true dose to the pulmonary epithelium from which lung cancer arises. Both length of employment and period of hire could be correlated with the time interval for dose integration. The substantial increase in risk over all dose categories after adjusting for the length of the dose integration interval (Table 22) and the inverse relation between this interval and risk suggests that the CINDY code has overestimated lung doses disproportionately for control subjects with high cumulative lung doses.

When computing doses with the CINDY code, professional judgement is used in selecting model parameters. Choices for the combination of solubility classes for plutonium and uranium isotopes, the time of first intake, and the internal distribution model selected are strongly based on the ability of the model

to estimate urine concentrations that replicate those that were measured. If the solubility of inhaled plutonium or uranium (there were no exposures by wound contamination in this group of cases and controls) changed over the operational history of the plant, and the model and modeler were more likely to make an error in dose estimation for one solubility class compared with another, then the error in dose estimation would be different for the two time periods. Such a difference could be correlated with period of first hire.

There is a new ICRP lung model (ICRP Publication 66 [ICRP, 1993]) that promises to improve estimates of lung dose over those made with the one implemented by the CINDY code. We are developing a computer code for implementing this model through a NIOSH grant. This new code will also estimate uncertainties of doses. We think improvements in dose estimates and their uncertainties will help interpret dose-response relations in future analyses.

Regardless of whether we can ever explain the forementioned confounding, it is clear that epidemiologic studies of plutonium workers need to account for a number of possible confounding variables in dose-response analyses. They must also be designed to reduce selection bias for any comparison group. To date, published studies of relations between dose and risk for lung cancer among plutonium workers have not included such variables.

Conclusions and Recommendations

The case-control study identified a risk for lung cancer from internal lung doses from exposure to plutonium and other radionuclides. In models with all study subjects, the odds ratios did not increase with increases in dose at cumulative doses above 400 mSv. When analyses were restricted to subjects who were employed for 15-25 years, the odds ratios increased with dose over all categories, with a statistically significant linear trend. Our results suggest that risks for lung cancer are different for those workers employed for short and long periods. The risk for lung cancer from cumulative internal lung dose is also confounded by the calendar period of first hire. We identified age at first internal lung dose as a risk factor, with older ages at first dose having higher odds ratios. Additional research is needed to explain these findings and to adjust for their influence on estimates of excess lung cancer risk per unit of cumulative internal lung dose.

We did not find evidence of a risk for lung cancer from doses of external penetrating radiation. Although our data showed smoking frequency was strongly related to lung cancer risk, smoking frequency did not confound the relation between cumulative internal lung dose and lung cancer mortality.

Our findings of low SMRs for most cancers are consistent with the strong healthy worker effect noted in other studies of nuclear workers. The significant increase noted for unspecified nervous system neoplasms as well as the increase for brain and other CNS cancers deserves further exploration. Since dosimetry models indicate that plutonium exposures deliver extremely small doses to the brain, other agents such as gamma photons, neutrons and chemical carcinogens should be considered as possible causes—singly and in combination.

Because plutonium inhalation can deliver doses to the digestive tract and the SMRs for cancers of the stomach and rectum are much higher than those reported in other studies of nuclear workers, these cancers deserve further analysis.

To be of greatest value, future epidemiologic studies should be cohort-based to avoid selection bias and to provide an adequate number of subjects for dose-response analyses and control of confounding variables. Analyses of risks from internal exposures to plutonium and other radionuclides should be performed with doses estimated with codes that have incorporated recent improvements in dosimetry models. Analyses should also explore possible errors and uncertainties in internal dosimetry models.

Our research indicates that, with the previously suggested improvements, it will be possible to make estimates of excess lung cancer risk per unit internal dose for plutonium workers. Such estimates are important for interpreting similar data for Mayak workers and for assuring that current exposure regulations for plutonium workers are adequately protective.

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