<u>Revised </u>Final Performance Report

LUNG FIBROSIS IN PLUTONIUM WORKERS

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Division of Environmental and Occupational Health Sciences
National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206

Lee S. Newman, MD, MA,
Principal Investigator, Division of Environmental and Occupational Health Sciences,
National Jewish Medical and Research Center, Denver, Colorado
Department of Medicine and Department of Preventive Medicine and Biometrics,
University of Colorado School of Medicine, Denver, Colorado

Margaret M. Mroz, M.S.P.H.
Department of Environmental and Occupational Health Sciences,
National Jewish Medical and Research Center, Denver, Colorado

A. James Ruttenber, PhD, MD
Co-Investigator, Department of Preventive Medicine and Biometrics,
University of Colorado School of Medicine, Denver, Colorado

Manuscript based on this report has been submitted for publication

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LIST OF ABBREVIATIONS

Sv = Sieverts (dose equivalent)

Gy = G ray unit (dose equivalent to 100 rads)

rad = radiation absorbed dose

Bq = Becquerel (activity)

Pu = plutonium

nCi = nanocurie

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SIGNIFICANT FINDINGS

There was a significantly higher proportion of abnormal chest radiographs among plutonium workers (17.5%) as compared to non-plutonium workers (7.2%), p = <0.01. Of those plutonium workers with absorbed lung doses greater than 10 Sv, 37.5% had an abnormal chest x-ray compared to other plutonium workers (16.5%), p = 0.04. When we controlled for effects of age, smoking and asbestos exposure, lung dose of 10 Sv or greater conferred a 5.3-fold risk of having an abnormal chest x-ray consistent with pulmonary fibrosis when compared to nonexposed individuals.

USEFULNESS OF FINDINGS

This study may lead to the description of a new source of lung morbidity in radiation workers, with potentially wide-reaching implications for both primary and secondary prevention of radiation-related, non-malignant lung disease.

ABSTRACT

Background: There have been few systematic studies of the non-malignant health effects of α-radiation in humans. Animal studies and a report from the former Soviet Union suggest an association between plutonium exposure and the development of fibrotic lung disease. Prompted by a case of lung fibrosis in a retired plutonium worker in the United States, we sought to explore whether plutonium inhalation increases the risk for developing chest radiograph abnormalities consistent with pulmonary fibrosis.

Methods: We conducted a retrospective study of nuclear weapons workers. Our study population consists of 326 plutonium-exposed workers with absorbed lung doses from 0 to 28 Sv and 194 workers who had no estimated plutonium exposure. Absorbed lung dose was calculated as part of an internal dose assessment. We compared severity of chest radiograph interstitial abnormalities between the two groups using the International Labour Organization (ILO) profusion scoring system.

Results: There was a significantly higher proportion of abnormal chest radiographs among plutonium workers (17.5%) as compared to non-plutonium workers (7.2%), $p = <0.01$. Of those plutonium workers with absorbed lung doses greater than 10 Sv, 37.5% had an abnormal chest x-ray compared to other plutonium workers (16.5%), $p = 0.04$. When we controlled for effects of age, smoking and asbestos exposure, lung dose of 10 Sv or greater conferred a 5.3-fold risk of having an abnormal chest x-ray consistent with pulmonary fibrosis when compared to nonexposed individuals.

Conclusions: Inhaled plutonium may cause lung fibrosis in humans at absorbed lung doses above 10 Sv.

Keywords: Plutonium, Pneumosclerosis, Fibrosis, Fibrotic Lung Disease, Pulmonary Fibrosis

INTRODUCTION

Despite more than 50 years of concern about the hazards of the α-particle-emitting radionuclide plutonium, primarily the isotope Pu-239, few toxic effects have been detected in exposed workers (1, 2). Although longitudinal studies show that inhaled plutonium causes chronic inflammatory lung disease and delayed-onset pulmonary fibrosis in experimental animals, epidemiologic studies have reported few non-malignant human health effects due to plutonium exposure (3-7). Investigators at Los Alamos National Laboratory (LANL) reported in 1997 that they found no significant health effects attributable to plutonium based on medical examinations performed on a small longitudinal case series (4), although the chest x-rays for these subjects were not systematically evaluated.

Other evidence suggests that plutonium may be associated with lung fibrosis. A cross-sectional study of 895 U.S. beryllium-exposed nuclear workers detected a cluster of eight cases of interstitial fibrosis not attributable to either beryllium disease or pneumoconiosis (8). In hindsight, six of these cases were former plutonium workers and three had measurable plutonium deposition in their lungs. A concurrent study of 518 beryllium-exposed ceramics workers with no plutonium exposure found no pulmonary fibrosis (9). Okladnikova and colleagues (3) reported 66 cases of "pneumosclerosis" (pulmonary fibrosis) in radiation workers at the Mayak facility in Russia who were exposed to plutonium in the 1950's. In that case series, absorbed doses to the lung exceeded 4.0 Gy (comparable to a dose of 80 Sv). An additional 54 cases of "pneumosclerosis of a combined genesis" were reported in individuals with absorbed lung doses "amounting to" 1.4 Gy (comparable to a dose of 28 Sv) (3). These researchers did not report how lung doses were estimated; nor did they indicate the range of doses over which plutonium might induce fibrosis in the lung.

Prompted by an index case of lung biopsy-documented fibrotic lung disease in a worker who previously inhaled plutonium particles in a U.S. nuclear weapons production accident, we investigated the hypothesis that plutonium workers at the Rocky Flats Plant near Denver, CO are at increased risk of developing chronic fibrotic lung disease due to the inhalation of plutonium.

Under the direction of the U.S. Department of Energy, the Rocky Flats plant produced nuclear weapons components for the U.S. Department of Defense from 1951 to 1989. Between these years approximately 18,000 workers were hired (10). Workers processed, cut and formed plutonium inside contained areas (glove boxes) to create detonators for nuclear weapons. Plutonium metal "buttons" were processed from plutonium nitrite. Both pure metal and scrap was melted, cast into ingots, rolled and pressed into parts that were then machined into precise shapes and welded together to form nuclear bomb cores (11). Though the glove boxes protected workers from most inhalational exposures, there were opportunities to be contaminated through cuts, puncture wounds, and through inhalational exposures as the result of explosions and fires. There were two major plutonium fires in the history of the plant: one in 1957 and another in 1969. Both contaminated many workers. Production of nuclear weapons components at Rocky Flats ceased in 1989. The plant is now in the process of decontamination and decommissioning.

Case Report: In December 1993, a 73-year old white male retired plutonium worker was referred for evaluation of an abnormal chest radiograph, detected through a former worker program that was screening for beryllium disease. He was symptomatic with cough and shortness of breath. From March 1952 until his retirement in 1982, the patient had worked at the Rocky Flats plant manufacturing triggers for nuclear weapons. In 1957, a reactor vessel disintegrated within a glove box, causing an explosion that resulted in his inhalation of plutonium oxide particles. Despite chelation therapy with calcium disodium ethylenediaminetetraacetate ($CaNa_2$ EDTA), he sustained a deposition of plutonium in the lungs that resulted in a cumulative equivalent lung dose of 23 Sv through 1993, with recently measured plutonium lung activity of 13.6 nCi. His medical, occupational, and environmental history suggested no other known cause of interstitial lung disease. He was a former smoker, quitting 9 years prior to his evaluation. At the time of his 1993 evaluation, his chest radiograph was abnormal, showing diffuse hazy opacities and bronchial wall thickening with an ILO profusion score of 1/1 with p/s opacities (12). Thin-section computed tomography of the thorax showed diffuse ground glass density, reticular opacities, and honeycombing (fibrosis) throughout all five lobes. There were no pleural plaques or effusions. Routine laboratory tests were normal with the exception of a mild lymphopenia. Antinuclear antibodies, rheumatoid factor, and anti-neutrophil cytoplasmic antibody levels were normal. The patient had a moderately severe gas-exchange abnormality that worsened with activity. Lung biopsies demonstrated interstitial fibrosis in a desquamative interstitial pneumonitis pattern, respiratory bronchiolitis with mural fibrosis, and secondary pulmonary vascular hypertensive changes consistent with severe pulmonary fibrosis. The lung pathology was consistent with the histologic changes and distribution similar to that observed in longitudinal studies of beagle dogs that have inhaled plutonium dioxide (PuO_2) (13-15). Blood and lavage beryllium lymphocyte proliferation tests (16) were both negative. The patient's lung biopsies showed no pathologic evidence of beryllium disease and energy dispersive x-ray microanalysis (EDXM) showed no increased amounts of silica, asbestos, or metals in the lung tissue. Clinical course had shown slowly progressive worsening of respiratory symptoms, restriction, gas exchange, poorly responsive to high dose oral corticosteroids.

METHODS

This study protocol was reviewed and approved by the Institutional Review Board at National Jewish Medical and Research Center. Two groups, plutonium exposed and unexposed, were chosen for the study. Plutonium-exposed individuals were drawn from a database of current and former employees who participated in a plant site radiation health program. Potential lung doses were determined using a computer model that calculated a crude estimate of plutonium lung dose based on activity in urine. Using these data, we randomly selected 280 employees with cumulative equivalent doses to the lung that were estimated to be greater than 1 Sv and 240 employees with equivalent doses to the lung estimated to be less than 1 Sv. Of the 520 plutonium-exposed individuals selected for the study, 326 (62.6%) had lung dose estimates calculated and available to the study. Although radiation exposure data (primarily measurements of plutonium concentrations in urine) were available on additional individuals, lung counts and absorbed dose calculations had not been performed. The lung doses for the 326 subjects were calculated using the Code for Internal Dosimetry software (17), which employs the International Commission on Radiological Protection Publication 30 lung dose model (18). With this

software, we estimated the magnitude of the plutonium intake at the time of an exposure incident, using curve-fitting methods to adjust model parameters so that modeled plutonium concentrations approximated measured plutonium concentrations in the urine that were measured periodically over employment and post-employment periods. Data from periodic lung counts were used to help estimate plutonium intake. From the intake estimate, the cumulative equivalent dose to the lung was calculated for the period of time after the date of intake to the date of the chest x-ray that was evaluated for this study.

Unexposed workers were chosen from a database originally constructed for a cohort study of Rocky Flats production workers (10). We selected workers who were born between 1909 and 1960, hired between 1951 and 1984 and had combinations of assigned buildings and job titles consistent with production work in order to match the birth and hire dates of the exposed individuals. From this population, we randomly selected an unexposed group comprised of 350 production workers who had never worked in a building that housed plutonium. After choosing the 350 potentially unexposed individuals based on work history, we had access to systemic deposition data to verify exposure. We used these systemic deposition data and excluded 156 individuals who had no data for evaluation or who had a systemic deposition that exceeded 30 Bq and potentially could have had an internal dose.

We retrieved the most recent chest radiograph that was available for each of the 520 subjects with verifiable exposure histories. Personal identifiers and demographic data were masked and the radiographs were randomly ordered and submitted to a panel of three National Institute of Occupational Safety and Health (NIOSH) certified B-readers who classified each radiograph according to the International Labour Organization (ILO) classification for radiographs of the pneumoconioses (12). We report the median interstitial lung small opacity profusion score of the three readers. A profusion score of 1/0 or greater is defined as abnormal.

Exposure to asbestos may also cause parenchymal abnormalities resulting in abnormal profusion scores. In the general population 80% - 90% of pleural plaques on chest x-ray are due to occupational exposure to asbestos (19). Because asbestos exposure estimates were not available for all of our study subjects, we used radiographic evidence of pleural abnormalities as a surrogate marker of asbestos exposure. The median response of the three B-readers was used to define pleural abnormalities consistent with asbestos exposure.

We used the chi-square, Fisher's Exact and Wilcoxon rank-sum tests for comparing frequencies of abnormal radiographs and other categorical variables between groups. We used the Student's t and Wilcoxon's sign-rank tests and analyses of variance for comparing continuous variables. For logistic regression modeling, we selected those variables from univariate analysis that were associated with abnormal profusion scores at a p-value of 0.25 or less. We treated lung dose as an indicator variable, using the following cut points: unexposed, exposed with lung dose less than 1 Sv, exposed with lung dose equal to 1 Sv and less than 5 Sv, lung dose 5Sv to less than 10 Sv, and lung dose 10 Sv or greater. All tests were implemented with PC SAS software (20), and all tests of statistical significance are two-tailed.

RESULTS

Chest x-ray data were available for all 326 individuals with lung dose estimates and all 194 of the unexposed individuals. The 520 study participants were predominantly male (97.7%) and nonHispanic white (95.7%) with a median age of 64.9 years (range 24.9 – 85.9 years) at time of chest radiograph. The plutonium-exposed and unexposed groups are compared in Table 1. There are no statistically significant differences in ethnicity, smoking habits, or hire year between exposed and unexposed participants. There were more non-Whites and more women in the unexposed group. The plutonium-exposed group was significantly older than the unexposed group at time of x-ray.

Smoking histories were available for 92% of the plutonium-exposed subjects but for only 43% of the unexposed subjects. Those without smoking data were significantly younger (mean age = 54.4 years) than those with these data (mean age = 62 years), p = <0.001). However, subjects 55 years of age and younger at time of chest x-ray showed no statistically significant differences in smoking habits when compared with the older subjects (data not shown).

The entire group of plutonium-exposed subjects had a significantly higher proportion of abnormal chest x-rays consistent with pulmonary fibrosis (17.5%) than did the non-exposed group (7.2%), (Table 1). When we controlled for the effects of age, sex and race in the logistic model, plutonium exposure conferred a 1.7-fold risk of having an abnormal profusion score [Odds Ratio (OR) = 0.9 – 3.3].

The risks of having an abnormal chest x-ray profusion score rose with increasing level of lung dose. In univariate logistic regression models, those in the lowest dose category (0 to less than 1 Sv) had a 2.8-fold risk of having an abnormal chest x-ray profusion score compared to the unexposed. This was higher than the 1.9 OR for subjects with doses from 1 Sv to less than 5 Sv. There was a 3.8-fold risk for those with doses from 5 Sv to less than 10 Sv. The highest dose group, those with cumulative lung doses 10 Sv or greater, had a 7.7-fold risk of having an abnormal chest x-ray compared to those in the control group (Table 2).

Age at time of chest x-ray was a significant risk factor for an abnormal chest-x-ray profusion, score with a 9% yearly increase in risk (Table 2). Ever-smokers had a 3.9-fold risk of having an abnormal profusion score compared to never-smokers. The presence of pleural abnormalities on chest x-ray, as a surrogate for asbestos exposure, conferred a 3.1-fold risk of having an abnormal profusion score.

In a logistic regression model that simultaneously controlled for age, smoking status and pleural abnormalities, subjects with cumulative lung doses 10 Sv or greater (range 10 Sv – 28 Sv) had a 5.3-fold risk of having an abnormal profusion score when compared with unexposed subjects. The risks dropped and were not statistically significant for the lower cumulative dose categories.

DISCUSSION

Cumulative lung dose from plutonium exposure of 10 Sv or greater was associated with chest x-ray abnormalities consistent with pulmonary fibrosis. Both univariate and multivariate analyses identified this statistically significant association even after adjusting for other known causes of lung fibrosis. Although the univariate analysis showed a dose-response relationship, a significant dose-response was not maintained when we controlled for the effects of age, smoking and asbestos exposure. This suggests that although high lung doses may be associated with pulmonary fibrosis, lower doses might not present a significant risk.

There are a number of known risk factors for pulmonary fibrosis. Increasing age and cigarette smoking both are risk factors, as well as numerous occupational exposures (21-24). Although we attempted to match plutonium exposed and unexposed groups on birth date and hire year, the plutonium-exposed individuals were eligible for a plant sponsored surveillance program for employees exposed to radiation. As part of this program, participants returned on a regular basis for chest x-rays and lung counts after termination. By comparison, the most recent chest x-rays on unexposed individuals were usually obtained at the time of termination, resulting in an age difference between our two groups. In univariate analyses, age at the time of chest x-ray was significantly associated with abnormal profusion scores. A 20-year age difference would result in 1.8-fold increase in risk. This finding is consistent with previous reports in the literature regarding the effect of age on the frequency of abnormal lung profusion scores (21-24). Iwai et al (24), investigating risk factors related to idiopathic pulmonary fibrosis (IPF) showed an approximate 1.3-fold risk for each 10-year increase in age group from 50 years to 80. Our group of participants with lung doses at or above 10 Sv had a median age of 69.5 compared to a median age of 59.6 among the unexposed, so age at time of chest x-ray played a significant role in the risk of having an x-ray reading consistent with pulmonary fibrosis.

Smoking is another known risk factor for pulmonary fibrosis in patients diagnosed IPF (21, 22, 25) and has been shown to contribute to abnormal chest x-ray profusion scores in studies of industrial workers (25). In our study, the odds ratio for ever having smoked was nearly as high as the odds ratio for the highest plutonium lung dose category and was statistically significant. The study was was limited by missing smoking data among the unexposed group. Smoking data were available for 92% of the plutonium-exposed individuals but for only 43% of the unexposed individuals. Since most exposed individuals came in for lung count evaluation, smoking data were updated on each visit. Older medical records from the plant did not indicate smoking status on many individuals. Those without smoking data were significantly younger (mean age = 54.4 years) than those with these data (mean age = 62 years), p = <0.001). However, subjects 55 years of age and younger at time of chest x-ray showed no statistically significant differences in smoking habits when compared with the older subjects.

Asbestos was probably the most common exposure associated with chest x-ray profusion abnormalities in this workforce. In both univariate and multivariate logistic regression models, the presence of a pleural abnormality was a statistically significant risk factor, suggesting that this variable is a reliable surrogate for asbestos exposure. The risk for an abnormal profusion score in a subject with pleural plaques is about half the risk for a cumulative lung dose of 10 Sv or greater, and less than the risk for having ever smoked.

Rocky Flats production workers, including our study subjects, were also at risk for exposure to beryllium. Beryllium causes a granulomatous and mononuclear cell interstitial lung disease in a small percentage of exposed individuals and may be difficult to distinguish from pulmonary fibrosis on chest radiograph (8, 9). Of all current and former workers who participated in medical surveillance at Rocky Flats, 1.6% have been diagnosed with this disease (26). In our study, only one of the 71 workers with an abnormal chest x-ray carried a diagnosis of CBD. This individual was part of the plutonium unexposed group. None of the participants in our study with plutonium lung doses of 10 Sv or greater carried a diagnosis of CBD and all had normal blood beryllium lymphocyte proliferation tests in beryllium medical surveillance, making the likelihood of disease misclassification small. Unfortunately, other workplace exposures, besides asbestos and beryllium, as well as medical exposures to radiation could not be evaluated.

Workers with lung doses at or above 10 Sv showed a 5.3-fold risk of having parenchymal abnormalities on chest x-ray, even after we controlled for the three most common risk factors for pulmonary fibrosis. In the report of pulmonary fibrosis at the Mayak facility (3), workers with evidence of pulmonary fibrosis reportedly had cumulative lung doses that ranged between 28 and 80 Sv. The authors provided no diagnostic criteria, no description of the methods used to estimate lung doses, no estimates of risk for lung disease per unit dose, and did not comment on the possible confounding by other exposures such as smoking and asbestos. It is therefore difficult to identify the lowest lung dose at which pulmonary fibrosis occurred. Our data suggest, however, that there is elevated risk at doses about three times lower than the lowest dose reported for Mayak workers.

It is important to note that few employees at this plant had high lung exposures. Fewer than 5% of plutonium exposed employees in this study had exposures of 10 Sv or greater. Plant personnel in the medical and dosimetry departments felt that most individuals with high lung doses would have been captured in this study.

The following lines of evidence support a causal relation between plutonium lung deposition and fibrotic lung disease. Inhaled plutonium, particularly the insoluble oxides to which Rocky Flats workers were usually exposed, remains in the lung for many years after inhalation (27-32). In the human lung, plutonium particles preferentially deposit in the respiratory and terminal bronchioles, peribronchiolar alveoli septi, and subpleural lymphatics (33, 34). Alpha-emitting "hot spots" can selectively deliver to small volumes of lung cells doses that are substantially higher than those estimated for the entire lung, and are sufficient to cause physiologic alterations and cell death in other species (31, 32, 35-37).

Many years after an initial low-level inhalation exposure to PuO_2, dogs can develop insidious onset of pulmonary fibrosis, inflammatory cell infiltration of alveolar septi, bronchiolar and alveolar cell hyperplasia and metaplasia, and subpleural lymphatic scarring with α-emitting particles trapped in the fibrotic areas (13-15, 38). Support for the link between plutonium and lung fibrosis in animals also comes from studies of baboons that inhaled PuO_2 and developed interstitial pneumonitis (39). Although we must exercise caution in extrapolating across animal species, the studies from multiple species support the thesis that humans can develop radiation pneumonitis and lung fibrosis long after initial deposition (40).

A report of eight plutonium workers in whom a delayed-onset fibrotic reaction developed in the basal layer of the epidermis surrounding retained α-emitting particles (41, 42) suggests that slowly progressive fibrosis can be elicited in human tissue following exposure to insoluble, retained plutonium (43). Although dose to the lung may differ from dose to the skin, it is reasonable to hypothesize that retention of such particles in the lungs may elicit a similar response, not unlike that observed in our index case.

Plutonium-induced fibrosis may not have been recognized in nuclear workers outside of Russia for a number of reasons. Like other forms of chronic lung injury, this disorder probably evolves slowly, delaying both the patient's and the physician's recognition of morbidity until late in the disease process, long after the patient has left the workforce. Clinical findings of a rare condition like pulmonary fibrosis are easy to confuse with other more common lung diseases, leading to misdiagnosis. Most clinicians do not take a sufficiently rigorous occupational and environmental work history to link work-related exposures to pulmonary fibrotic conditions. There is a paucity of medical literature concerning non-malignant health effects in plutonium workers. Most of the large epidemiologic investigations have focused on cancer mortality in radiation workers (10). Considering radiation as a possible etiologic agent, most clinicians are familiar with only acute radiation pneumonitis, a more obvious form that develops within a few weeks to a few years after exposure.

The clinical significance of plutonium-induced fibrosis remains to be determined. The pulmonary status of the Mayak workers has not been reported in the open literature. Reports of the clinical status of Mayak workers along with clinical evaluations of Rocky Flats workers with high lung doses from plutonium exposure would be useful in defining the clinical course of this disease. It is important to note that all individuals with lung depositions of plutonium in our study had acute inhalational exposures to plutonium readily traced back to accidents or equipment failure. We do not know if lower-level chronic exposure or repeated low-level inhalation exposures would produce the same radiographic evidence of fibrosis.

We suggest that physicians who treat nuclear workers consider plutonium exposure in patients with abnormal pulmonary findings. If a worker reports possible exposure to plutonium, records of radiation exposure should be requested from the facility where the exposure may have occurred. Review of these records by an expert in health physics will usually clarify the possibility of an exposure and the size of lung dose that could have been received. If records are missing or appear to be inadequate, then additional dose assessment may be required. Compensation programs for radiation-exposed nuclear weapons workers (44) should include pulmonary fibrosis in plutonium workers as a compensable condition.

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REFERENCES

1. Wilkinson, G. S., G. L. Tietjen, L. D. Wiggs, W. A. Galke, J. F. Acquavella, M. Reyes, G. L. Voelz, and R. J. Waxweiler. 1987. Mortality among plutonium and other radiation workers at a plutonium weapons facility. *Am J Epidemiol* 125:231-250.

2. Voelz, G. L. 1991. Health considerations for workers exposed to plutonium. *In* G. S. Wilkinson, editor. The Nuclear Energy Industry, Occupational Medicine State-of-the-Art Reviews. Hanley and Belfus, Inc., Philadelphia. 681-694.

3. Okladnikova, N. D., V. S. Pesternikova , M. V. Sumina, and V. N. Doshchenko. 1994. Occupational diseases from radiation exposure at the first nuclear plant in the USSR. *Sci Total Environ* 142:9-17.

4. Voelz, G. L., J. N. P. Lawrence, and E. R. Jonson. 1997. Fifty years of plutonium exposure to the Manhattan project plutonium workers: An update. *Health Physics* 73:611-619.

5. Hempelmann, L. H., W. H. Langham, C. R. Richmond, and G. L. Voelz. 1973. Manhattan Project plutonium workers: A twenty-seven year follow-up study of selected cases. *Health Physics* 25:461-479.

6. Voelz, G. L., G. S. Wilkinson, J. F. Acquavella, G. L. Tietjen, R. N. Brackbill, M. Reyes, and L. D. Wiggs. 1983. An update of epidemiologic studies of plutonium workers. In: Proceedings of the international meeting on the radiobiology of radium and the actinides in man, Lake Geneva, Wisconsin, October 11-16, 1981. *Health Physics* 44((Suppl 1)):493-503.

7. Voelz, G. L., and J. N. P. Lawrence. 1991. A 42-year medical follow-up of Manhattan Project plutonium workers. *Health Physics* 61:181-190.

8. Kreiss, K., M. M. Mroz, B. Zhen, J. Martyny, and L. S. Newman. 1993. Epidemiology of beryllium sensitization and disease in nuclear workers. *Am Rev Respir Dis* 148:985-991.

9. Kreiss, K., S. Wasserman, M. M. Mroz, and L. S. Newman. 1993. Beryllium disease screening in the ceramics industry. Blood lymphocyte test performance and exposure-disease relations. *J Occup Med* 35(3):267-74.

10. Ruttenber, A., M. Schonbeck, J. McCrea, D. McClure, and J. Martyny. 2001. Improving estimates of exposures for epidemiologic studies of plutonium workers. *In* G. Wilkinson, editor. Occupational Medicine: State of the Art Reviews. Hanley & Belfus, Inc., Philadelphia.

11. Ackland, L. 1999. Making a real killing: Rocky Flats and the nuclear west. University of New Mexico Press, Albuquerque.

12. ILO. 1980. Guidelines for the use of ILO international classification of radiographs of pneumoconioses. *International Labour Office (Occupational Safety and Health Series, No. 22 [REV]).*

13. Clarke, W. J., and W. J. Bair. 1964. Plutonium inhalation studies-VI: Pathologic effects of inhaled plutonium particles in dogs. *Health Physics* 10:391-398.

14. Park, J. F., W. J. Clarke, and W. J. Bair. 1964. Chronic effects of inhaled plutonium in dogs. *Health Physics* 10:1211-1217.

15. Park, J. F., W. J. Bair, and R. H. Busch. 1972. Progress in beagle dog studies with transuranium elements at Battelle-Northwest. *Health Physics* 22:803-810.

16. Mroz, M. M., K. Kreiss, D. C. Lezotte, P. A. Campbell, and L. S. Newman. 1991. Re-examination of the blood lymphocyte transformation test in the diagnosis of chronic beryllium disease. *J Allergy Clin Immunol* 88:54-60.

17. Battelle. 1992. Code for internal dosimetry: CINDY Version 1.2., Part 1: Conceptual Representation. *Battelle Memorial Institute* PNL-7493, PT. 1, Rev. 1 (July).

18. 1986. ICRP Publication 30, Limits for intakes of radionuclides by workers. *Ann ICRP*.

19. Hillerdal, G. 1997. Radiological criteria: pleural changes. Proceedings of an international expert meeting, People and work research reports no. 14. Asbestos, asbestosis and cancer. Finnish institute of occupational health, Helsinki, Finland.

20. 1992. SAS Institute, Inc. SAS Technical Report P-229, Software: Changes and Enhancements, Release 6.07, Cary, North Carolina. 287-366.

21. Baumgartner, K. B., J. M. Samet, C. A. Stidley, T. V. Colby, and J. A. Waldron. 1997. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 155(1):242-8.

22. Baumgartner, K. B., J. M. Samet, D. B. Coultas, C. A. Stidley, W. C. Hunt, T. V. Colby, and J. A. Waldron. 2000. Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. *Am J Epidemiol* 152(4):307-15.

23. Coultas, D. B., R. E. Zumwalt, W. C. Black, and R. E. Sobonya. 1994. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 150(4):967-72.

24. Iwai, K., T. Mori, N. Yamada, M. Yamaguchi, and Y. Hosoda. 1994. Idiopathic pulmonary fibrosis. Epidemiologic approaches to occupational exposure. *Am J Respir Crit Care Med* 150(3):670-5.

25. Weiss, W. 1988. Smoking and pulmonary fibrosis. *J Occup Med* 30(1):33-9.

26. Stange, A. W., D. E. Hilmas, F. J. Furman, and T. R. Gatliffe. 2001. Beryllium sensitization and chronic beryllium disease at a former nuclear weapons facility. *Appl Occup Environ Hyg* 16(3):405-17.

27. Bair, W. J., J. E. Ballou, J. F. Park, and C. L. Sanders. 1974. Plutonium in soft tissues with emphasis on the respiratory tract. *In* H. C. Hodge, J. N. Stannard and J. B. Hursh, editors. Uranium, Plutonium, and Transplutonic Elements. Springer-Verlag, New York. 503.

28. Foreman, H., W. Moss, and W. Langham. 1960. Plutonium accumulation from long-term occupational exposure. *Health Physics* 2:326-333.

29. Lagerquist, C. R., S. E. Hammond, D. L. Bokowski, and D. B. Hylton. 1973. Distribution of plutonium and americium in occupational exposed humans as found from autopsy samples. *Health Physics* 25:581-584.

30. Newton, D., B. T. Taylor, and J. D. Eakins. 1983. Differential clearance of plutonium and americium oxides from the human lung. *Health Physics* 44((Suppl 1)):431-439.

31. Cottier, H., F. Meister, A. Zimmerman, R. Kraft, A. Burkhardt, P. Gehr, and G. Poretti. 1987. Accumulation of anthracotic particles along lymphatics of the human lung: Relevance to "hot spot" formation after inhalation of poorly soluble radionuclides. *Radiat Environ Biophys* 26:275-282.

32. Simmons, J. A., and S. R. Richards. 1984. Microdosimetry of alpha-irradiated lung. *Health Physics* 46:607-616.

33. Bair, W. J., and R. C. Thompson. 1974. Plutonium: Biomedical research. *Science* 183:715-722.

34.   Sanders, C. L., K. E. Lauhala, and K. E. McDonald. 1989. Quantitative scanning electron microscopic autoradiography of inhaled ^{239}PuO$_2$. *Health Physics* 56:321-325.

35.   Bair, W. J., and B. J. McClanahan. 1961. Plutonium inhalation studies. II. Excretion and translocation of inhaled ^{239}PuO$_2$ dust. *Arch Environ Health* 2:48-55.

36.   Anonymous. 1974. Editorial: Hot spots or hot lungs? *Lancet* 2:1238-1239.

37.   Lloyd, E. L., M. A. Gemmel, C. B. Henning, D. S. Gemwell, and B. J. Zabransky. 1979. Cell survival following multiple-track alpha irradiation. *Int J Radiat Biol* 35:23-31.

38.   Yuile, C. L., R. F. Gibb, and P. E. Morrow. 1970. Dose-related local and systemic effects of inhaled plutonium-238 and plutonium-239 dioxide in dogs. *Radiat Res* 44:821-834.

39.   Bair, W. J., H. Metivier, and J. F. Park. 1980. Comparison of early mortality in baboons and dogs after inhalation of ^{239}PuO$_2$. *Radiat Res* 82:588-610.

40.   Muggenburg, B. A., R. K. Wolff, J. L. Mauderly, M. M. Plaggmier, F. F. Hahn, R. A. Guilmette, and R. F. Gerlach. 1988. Cardiopulmonary function of dogs with plutonium-induced chronic lung injury. *Radiat Res* 115:314-324.

41.   Lushbaugh, C. C., and J. M. Langham. 1962. A dermal lesion from implanted plutonium. *Arch Dermatol* 86:461-464.

42.   Lushbaugh, C. C., R. J. Cloutier, and G. Humason. 1967. Histopathologic study of intradermal plutonium metal deposits: Their conjectured fate. *Ann NY Acad Sci* 145:791-797.

43.   Voelz, G. L. 1975. Plutonium — health implications for man: What we have learned about plutonium from human data. *Health Physics* 29:551-561.

44.   DOL (U. S. Department of Labor), 2001. 20 CFR Parts 1 and 30, Performance of functions under this chapter; claims for compensation under the energy employees occupational illness compensation program act; final rule. *Federal Register* 66(102):28948.

Table 1. Demographic Results at Time of Chest Radiograph for Plutonium-exposed and Unexposed Workers, Rocky Flats Plant (2002).

Variable	Plutonium Exposed		Plutonium Unexposed		*P**
	N	Median	N	Median	
Age at chest x-ray	326	68.1	194	59.6	<0.01
Length of employment (yr)	326	37.7	194	26.8	<0.01
Year of hire	326	1957	194	1958	0.16
	N	%	N	%	*P*†
Sex					
Male	326	100	182	93.8	<0.01
Female	0	0	12	6.2	
Race					
White	321	99.4	184	96.3	0.04
Non-white	2	0.6	7	3.7	
Ethnicity					
Hispanic	7	2.2	6	3.1	0.60
Non-Hispanic	316	97.8	185	96.9	
Smoking status					
Current	32	10.7	10	12.1	
Former	174	58.0	50	60.2	0.80
Never	94	31.3	23	27.7	
Missing	26	8.0	111	57.0	<0.01
Chest X-ray profusion score					
Abnormal	57	17.5	14	7.2	<0.01
Normal	269	82.5	180	92.8	

*Wilcoxon rank-sum test
†Chi-square test

Table 2: Odds Ratio Estimates for Logistic Regression Model of Variables Predictive of Abnormal Chest X-ray Profusion Score.

Variable	N	Abnormal Chest Profusion Scores %	Univariate OR	95% CI	Adjusted* OR	95% CI
Cumulative lung dose (Sv)						
Unexposed	194	7.2	---	---	---	---
Exposed ≥0, <1	187	17.6	2.8	1.4 – 5.3	1.5	0.6 – 3.8
≥1, <5	101	12.9	1.9	0.9 – 4.2	0.9	0.3 – 2.6
≥5, <10	22	22.7	3.8	1.2 – 11.8	1.7	0.5 – 6.6
≥10	16	37.5	7.7	2.4 – 24.3	5.3	1.2 – 23.4

	Pu-Exposed		Unexposed					
Median Age (Years)=	68.1		59.6		1.09	1.05 – 1.13	1.07	1.03 – 1.11
	N	%	N	%				
Smoking status								
Ever	206	68.7	60	72.3	3.9	1.7 – 8.9	4.2	1.8 – 10.0
Never	94	31.3	23	27.7				
Pleural abnormality								
Present	88	27.9	9	5.0	3.1	1.7 – 5.5	2.4	1.2 – 4.5
Absent	228	72.1	170	95.0				

* model adjusted for age at chest x-ray, smoking, and presence of pleural abnormalities

=   age at time of chest x-ray

LIST OF PRESENT AND POSSIBLE FUTURE PUBLICATIONS

Newman L.S., Mroz M.M., Ruttenber A.J. 2002. Lung Fibrosis in Plutonium Workers. *Lancet* (submitted)