Final Performance Report

LUNG FIBROSIS IN PLUTONIUM WORKERS

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LIST OF ABBREVIATIONS

rem = roentgen equivalent man (dose equivalent)

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

rad = radiation absorbed dose

Pu = plutonium

nCi = nanocurie

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SIGNIFICANT FINDINGS

There was a significantly higher proportion of abnormal chest radiographs among plutonium workers (17.4%) as compared to unexposed workers (7.2%). Plutonium workers were older at time of x-ray than were unexposed workers. However, the proportion of plutonium workers with abnormal chest x-rays remained significantly higher when we restricted analyses to those individuals older than 60 years. Of those plutonium workers with absorbed lung doses greater than 500 rem, 29% had an abnormal chest x-ray compared to other plutonium workers (16%). This increased risk remained even when we controlled for smoking. These findings suggest that inhaled plutonium may cause lung fibrosis in humans at lung doses above 500 rem.

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 recent 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. To date, our study population consists of 327 plutonium-exposed workers with absorbed lung doses from 0 to 2,800 rem and 194 workers who had no estimated plutonium exposure. Participants were predominantly male (97.6%) with a mean age of 63.8 years. There were no significant differences in time working at the plant, hire year, or smoking habits between the two groups, although plutonium workers were older at the time of chest x-ray (67. 4 years vs. 57.7 years). Absorbed lung dose was calculated as part of an internal dose assessment. We compared severity of posteroanterior chest radiograph interstitial abnormalities between the two groups using the International Labour Organization (ILO) profusion scoring system.

Findings: There was a significantly higher proportion of abnormal chest radiographs among plutonium workers (17.4%) as compared to non-plutonium workers (7.2%), $p = <0.01$. Plutonium workers were older at time of x-ray then were unexposed workers. However, the proportion of plutonium workers with abnormal chest x-rays remained significantly higher when we restricted analyses to those individuals older than 60 years. Of those plutonium workers with absorbed lung doses greater than 500 rem, 29% had an abnormal chest x-ray compared to other plutonium workers (16%), $p = 0.06$.

Interpretation: Inhaled plutonium may cause lung fibrosis in humans at absorbed lung doses above 500 rem.

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, few epidemiologic studies have examined the non-malignant human health effects of plutonium [2-9]. Investigators at Los Alamos National Laboratory (LANL) reported in 1997 that they found no significant health effects attributable to plutonium based on a small longitudinal case series [2,4-6].

Other evidence suggests that plutonium may be associated with lung fibrosis. A cross-sectional study of 895 beryllium-exposed nuclear workers detected a cluster of eight cases of interstitial fibrosis not attributable to either beryllium disease or pneumoconiosis [10]. 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 [11]. Okladnikova and colleagues, from the former Soviet Union, reported 66 cases of "pneumosclerosis" (pulmonary fibrosis) in radiation workers who were exposed to plutonium in the 1950's that resulted in equivalent doses to the lung exceeding 4.0 Gy (dose equivalent = 8,000 rem) and 54 cases of pulmonary fibrosis in individuals with internal lung doses averaging 1.4 Gy (dose equivalent = 2,800 rem) but who had other possible etiologies [3].

Prompted by an index case of lung biopsy-documented fibrotic lung disease in a worker who previously inhaled plutonium particles in an industrial accident, we investigated the hypothesis that plutonium workers are at increased risk of developing chronic fibrotic lung disease due to the inhalation of plutonium or other toxic compounds.

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 workplace surveillance program for beryllium disease. He was symptomatic with cough and shortness of breath. From March 1952 until his retirement in 1982 the patient worked at the Rocky Flats plant in Golden, Colorado, USA manufacturing triggers for nuclear weapons. In 1957, while working with plutonium in a glove box, a reactor vessel disintegrated 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 lung that resulted in a cumulative equivalent lung dose of 2,300 rem 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. 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. 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 observed in longitudinal studies of beagle dogs that have inhaled plutonium dioxide (PuO_2) [12-14]. The patient showed no evidence of beryllium disease and energy dispersive x-ray microanalysis (EDXM) showed no increased amounts of silica, asbestos, or metals in the lung tissue.

METHODS

Our study consisted of two groups, 1) employees of a nuclear weapons facility (Rocky Flats) who had never worked in a plutonium building and 2) employees of the same facility who had the potential to have an absorbed plutonium lung dose. Workers without plutonium exposure were chosen from a database which reconstructed job and building histories for all workers employed in plant history. We restricted selection to all workers born between 1909 and 1960, hired between 1951 and 1984 and those individuals employed in production jobs/areas. We randomly selected 350 workers who had never worked in a plutonium building for group 1. Group 2 consisted of three subgroups; a) 125 randomly selected individuals who had worked in a plutonium building but who were not known to have a potential lung dose of plutonium; b) 280 employees with a potential high lung exposure (greater than 100 rem) and c) 240 employees with a potential low lung dose (greater than 0 rem but less than 100 rem). The latter two groups were randomly chosen from 745 records of current and former employees in whom lung dose of plutonium had been estimated by the plantsite radiation health program.

Since the 1960's Rocky Flats has measured plutonium systemic deposition and lung activity for former and current workers identified as having internal depositions of this radionuclide. The plant has maintained detailed radiation dosimetry records consisting of systemic and lung deposition estimates made from urinalysis and *in vivo* lung count data; fecal analysis for plutonium; wound counts; incident/accident reports; as well as film and thermoluminescent external dosimetry data since the beginning of production in 1952. Lung doses were calculated for the workers with plutonium lung depositions using a computer model [15] which estimated the magnitude of the intake at the time of the exposure incident by applying curve fitting methods to the observed data. From the intake data, the model then calculated the equivalent dose to the lungs, as well as to other organs, for the period of time after the date of intake to the date of the most recent in-vivo lung measurement. Lung dose in rem to date of chest x-ray was calculated for study individuals. The model is unable to distinguish whether lung count data represent lung tissue deposition of plutonium via inhalation or deposition in the mediastinal lymph nodes from contaminated wounds.

We retrieved the most recent chest radiograph available for each of the subjects. Personal identifiers and demographic data were masked and the radiographs were randomly collated 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 [16]. We reported the median opacity profusion score of the three readers. A profusion score of 1/0 or greater is defined as abnormal.

We used chi-square, Fisher's Exact test , Wilcoxon's rank sum test for comparing frequencies of abnormal radiographs and other categorical variables between groups. We used Student's t-test and Wilcoxon's sign rank test and analyses of variance for comparing continuous variables. We chose a significance level of 0.05. For logistic regression we used PC SAS and chose variables from univariate analysis that were associated with abnormal chest x-rays. All tests were two-tailed.

RESULTS

Exposure data and chest x-ray readings were available on 327 (50.7%) of the plutonium exposed individuals. All 327 had an estimate of plutonium absorbed lung dose calculated to time of x-ray. Systemic burden estimates based on urine data were available to verify exposure on the plutonium-unexposed individuals. Chest x-ray data were available on 194 (55.4%) of the unexposed individuals who had no history of work in a plutonium building and had systemic burden estimates less than or equal to 0.02 rem. Data collection on the other 474 individuals is in progress. The 521 current study participants are predominantly male (97.7%) and nonHispanic white (95.7%) with a mean age of 63.8 years at time of chest radiograph. The plutonium-exposed and unexposed groups are compared in Table 1. There were no statistically significant differences in Hispanic ethnicity, smoking habits (available on 74.5% of participants), tenure at the plant, 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 older at time of x-ray than was the unexposed group.

Plutonium-exposed subjects had a significantly higher proportion of abnormal chest x-rays (17.4%) than did the non-exposed group (7.2%), $p = 0.0006$ (Table 2). Since there were significantly more nonWhites and more women in the unexposed group, we removed them from analysis and found no difference, with an abnormal chest x-ray rate among plutonium-exposed of 17.5% compared to a rate of 8.0% among unexposed ($p = 0.002$). The plutonium-exposed individuals were also significantly older than were the unexposed group. Therefore we restricted the analysis to all subjects older than 60 years ($n = 376$). There was still a significant difference in proportion of abnormal x-rays among the plutonium-exposed individuals (19.9%) compared to unexposed individuals (6.9%), $p = 0.03$. However, even in this restricted analysis, the plutonium-exposed group was statistically significantly older, with a mean age of 69.6 years compared to a mean age of 66.9 years for unexposed.

There were no differences in smoking status between plutonium-exposed and unexposed to account for the difference in proportion of abnormal x-rays but this analysis 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. Those without smoking data were significantly younger (mean age = 54.4 years) than individuals with smoking data (mean age = 62 years), $p = <0.001$). To examine whether those of younger age may have different smoking habits in this group we looked at those with smoking data who were younger and older than 55 years. Individuals 55 years and younger had no significant differences in smoking habits than older participants, although the younger group had a higher proportion of never smokers (42% compared to 30%) and a higher proportion of current smokers (16% compared to 10%). If the true proportion of current and former smokers is significantly higher among the plutonium-exposed group as compared with the unexposed group, then the difference seen in the proportion of abnormal chest x-rays may be partly attributable to smoking, however current data do not show an association.

Among the 327 plutonium-exposed workers, we observed an increased proportion of abnormal radiograph profusion scores among the workers with an absorbed plutonium lung dose greater than 500 rem. Of the 38 workers with calculated lung doses between 500 rem and 2,800 rem, 29% had abnormal chest x-rays compared with an abnormal chest x-ray

proportion of 16% among those with lower doses, p = 0.06 (Table 2). There were no statistically significant differences in age or smoking habits between the high and lower lung dose groups. However, there was a higher proportion of ever-smokers among those with high absorbed lung dose compared to those with a lower lung dose (78.8% verses 67.4%, p = 0.11). A logistic regression model which included ever-smoking, high lung dose and an interaction between smoking and lung dose determined that both smoking and high absorbed lung dose contributed equally to an increased risk of abnormal chest x-ray (Table 3). The odds ratio of abnormal chest x-ray for those with high lung dose was 4.6, the same as was the odds ratio of abnormal chest x-ray among ever-smokers. There was no interaction between smoking and high lung dose. In addition, there was no correlation between absolute lung dose and rank of ILO profusion score.

DISCUSSION/CONCLUSIONS

These preliminary data suggest a relationship between plutonium exposure and chest x-ray abnormalities in nuclear workers (Data collection and analysis is still in progress as of the time of this report). However, the difference in the proportion of chest x-ray abnormalities may be attributable to the older age at time of chest x-ray for plutonium-exposed individuals. Plutonium-exposed individuals were likely to be part of a radiation surveillance project on plantsite that brought them back for lung counting and clinical evaluation which included chest x-ray. Unexposed individuals were not eligible for this program. Controlling for age (> 60 years) we still observed a significant difference in proportion of abnormal chest x-rays between groups, however the plutonium-exposed individuals were still slightly, though significantly older with a mean age of 69.6 years compared to 67.0 years in the unexposed group. This difference may not be biologically significant, however. The difference in proportion of abnormal x-rays among plutonium-exposed and unexposed groups was not evident when we looked at the subset of those 60 years and younger. These analyses suggest that age may contribute to the increased rate of chest x-ray abnormalities among the plutonium-exposed group.

The higher proportion of chest x-ray abnormalities (29%) among those with lung doses greater than 500 rem compared to those with lower lung exposures (0 to 499 rem) suggests that very high doses of plutonium may be associated with chest x-ray abnormalities. In this model, there were no significant differences in age or smoking habits between the high lung dose group and others, though those with high absorbed lung dose tended to be ever-smokers. When controlling for smoking, high lung dose continued to be a significant risk factor for chest x-ray abnormalities consistent with pulmonary fibrosis.

The single published study to date that suggests an association of pulmonary fibrosis and inhaled plutonium in humans formed a small part of a report by Okladnikova and colleagues [3]. They described 66 cases of pulmonary fibrosis in radiation workers exposed to plutonium in the 1950's resulting in lung dose equivalents exceeding 8,000 rem and 54 cases of pulmonary fibrosis in individuals with lung dose equivalents as high as 2,800 rem but who had other possible causes. These significant radiation exposures were attributed to the dangerous conditions occurring in the start-up period of the Mayak nuclear facility in the former Soviet Union. Scant details were provided in this report.Most affected individuals were female. Our study found a relationship between acute inhalation of plutonium and delayed onset of chest radiographic abnormalities consistent with pulmonary fibrosis resulting from lung doses between 500 rem and 2,800 rem which were not attributable to age and separate from smoking. The results of both of these studies suggest that lung deposition of plutonium can cause fibrotic lung disease in humans. There may be other exposures that could lead to pulmonary fibrosis, as work at the plant involved numerous other metals and chemicals. However, the non-exposed worker group was drawn from a population of individuals exposed to other production processes which include beryllium, which is known to cause granulomatous lung disease in this plant and which can be difficult to distinguish from pulmonary fibrosis on chest radiograph [10,11]. This group also worked in different areas and jobs than did the exposed workers, and may have encountered other exposures that might have led to abnormal chest radiographs. Thus, our high background rate of abnormal

radiographs in the unexposed worker group may have led to an under-estimate of the plutonium-associated risk. On the other hand, we may have overestimated the rate of abnormal chest radiographs among workers with plutonium lung depositions. Although not statistically significant, there was a tenency toward a higher proportion of current smokers with high absorbed lung doses (greater than 500 rem). It can be difficult to determine if abnormalities seen on chest x-ray are due to deposition of plutonium via inhalation or are due to smoking.

The following lines of evidence support an association between plutonium lung deposition and fibrotic lung disease. The lungs are the most significant route of entry, deposition, and systemic absorption of plutonium in humans. Although the amount of plutonium absorbed by, and retained in, human lung varies, a sizable proportion remains in the chest of inhalationally-exposed plutonium workers throughout their lives (17). The more insoluble forms, like Pu O_2, were commonly encountered by the workers in our study and are poorly cleared from the lungs (17-22). Notably, inhaled plutonium particles deposit non-uniformly in the human lung, favoring respiratory and terminal bronchioles, peribronchiolar alveoli septi, and subpleural lymphatics (23,24). Alpha-emitting "hot spots" selectively expose small volumes of lung cells and tissue to locally higher radiation doses, sufficient to cause physiologic alterations and cell death in other species (21,22,25-27).

A number of well-designed, longitudinal studies have examined the long-term pathologic, physiologic, and radiographic consequences of plutonium inhalation in several animal species, especially canines. The pulmonary and systemic fates of plutonium in humans and dogs share many similarities. 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 (12-14,28). 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 (29). Although we must exercise caution in extrapolating across animal species, the studies from multiple species support the thesis that "people exposed to aerosols of relatively insoluble plutonium resulting in moderately high lung deposition could develop radiation pneumonitis and lung fibrosis at relatively long times after exposure" (30).

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 (31,32) suggests that slowly progressive fibrosis can be elicited in human tissue following exposure to insoluble, retained plutonium (33). Although dose to the lung may differ from dose to skin cells, it is reasonable to hypothesize that retention of such particles in the lungs may elicit a similar, patchy response, not unlike that observed in our index case.

The relationship between low-level lung exposure to radionuclides and pulmonary fibrosis has not been recognized until now for several 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. 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 animal research demonstrates that the pattern of respiratory tract effects of inhaled α-emitters differ from the clinical and pathologic effects produced by external beam radiation exposures.

We continue to gather and analyze data for this study. Expanding the data set for range of plutonium lung deposition may help to better define the dose-response relationship between lung exposure and chest radiograph severity. Good dosimetry is essential to estimate lung doses of plutonium. Comparing the Okladnikova data set with our data would also be helpful in examining the full spectrum of plutonium-related fibrosis. In addition, examining biopsy materials specifically from plutonium-exposed humans may contribute to an understanding of the pathogenesis of lung fibrosis due to plutonium exposure.

All individuals with lung depositions of plutonium in our study had acute inhalational exposures 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 fibrogenic effect. It is possible that hazardous waste workers and individuals in other industries where there is potential exposure to low-level cumulative doses of α-emitters may be at-risk. In conclusion, general physicians, occupational medicine and pulmonary specialists need to be aware of this new, probable cause of pulmonary fibrosis in patients who have worked in the U.S. nuclear weapons industry.

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Table 1. Demographic Results at Time of Chest Radiograph for Plutonium-exposed and Unexposed Workers, Rocky Flats Plant (1999).

	Plutonium-exposed Workers	Non-exposed Workers
Mean age in years (s.d.)*	67.5 (7.9)	57.7 (11.8)
Gender (% male)*	100.0	93.8
Race (% white)*	99.4	96.3
Ethnicity (% Hispanic)	2.2	3.1
Mean tenure at the plant in years (s.d.)	25.2 (9.3)	25.3 (8.3)
Median Hire Year	1957	1958
Smoking (%): Current smoker	10.7	12.1
Former smoker	58.0	60.2
Never smoker	31.3	27.7

* significant difference with $p < 0.05$

Table 2. Frequency of Abnormal Chest Radiograph Profusion Scores, Plutonium Exposed Worker Study , Rocky Flats Plant (1999).

Group	Frequency of Abnormal Radiographs*, n (%)
1) Plutonium workers	57/327 (17.4)
1a) Plutonium workers with plutonium lung deposition > 500 rem	11/38 (28.9)
1b) Plutonium workers with plutonium lung deposition < 500 rem	46/289 (15.9)
2) Unexposed workers	14/194 (7.2)

* Defined as a median profusion score $\geq$ 1/0 of three ILO classification certified B-readers.

Table 3: Logistic Regression Model of Variables Predictive of Abnormal Chest x-ray

Independent variables	Parameter Estimates	OR (95% CIs)	P value
Intercept	-5.4785		
Ever smoking	1.5210	4.6 (2.1 – 9.8)	0.0001
High Pu lung dose (>500 rem)	1.5330	4.6 (1.1 – 19.5)	0.0367
Ever smoking x high lung dose	-0.2516	0.8 (0.02 – 1.1)	0.1310

LIST OF POSSIBLE FUTURE PUBLICATIONS

1) Lung Fibrosis in Plutonium Workers

   (the above report with all analyses completed)

2) Lung Fibrosis Related to Plutonium Exposures and Other Chemical Exposures Using a Job Exposure Matrix

   (an extension of the previous study incorporating chemical exposure information from a site-specific job-exposure matrix)