Memorandum

Date: January 22, 2004

From: Susan B. Board, Program Official
Office of Extramural Programs, NIOSH, E-74

Subject: Final Report Submitted for Entry into NTIS for Grant 5K01OH000181-03.

To: William D. Bennett
Data Systems Team, Information Resources Branch, EID, NIOSH, P03/C18

The attached final report has been received from the principal investigator on the subject NIOSH grant. If this document is forwarded to the National Technical Information Service, please let us know when a document number is known so that we can inform anyone who inquires about this final report.

Any publications that are included with this report are highlighted on the list below.

Attachment
cc: Sherri Diana, EID, P03/C13

List of Publications

Takaro TK, Griffith WC, Omri K, Checkoway Hand Faustman EM. Asbestos and radiation as combined exposures in pulmonary fibrosis. Toxicologist N: 42.2003 (abstract).

Title: Combined Effect Of Radiation & Asbestos In Producing Pul
Investigator: Timothy Takaro
Affiliation: University Of Washington
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Telephone: (206) 616-7458
Award Number: K01OH181
Start & End Date: 7/1/1999-6/30/2003
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Program Area:
Key Words: asbestos, mixed exposures, radiation

Final Report Abstract:

RATIONALE: Workers exposed to asbestos may encounter radiation as radon or from other sources. Both asbestos and radiation are etiologic agents in pulmonary fibrosis. The aim of this study is to determine whether concomitant radiation exposure in asbestos workers increases the incidence of pulmonary fibrosis.

METHODS: 2263 asbestos exposed former nuclear weapons workers from a medical surveillance program form the study cohort. PA chest radiographs and spirometry were performed for screening. Fibrosis was defined by B-read opacity profusion category on chest radiographs ?:. 1/0, or spirometric evidence of restrictive or mixed disease. The cohort is largely male (91.0%) with an average age of 63.3 years. 1157 workers had complete work histories, including external radiation badge doses and laboratory data.

RESULTS: The demographic and fibrosis endpoints were similar in the entire cohort vs. the 1157 analyzed. Asbestos exposure based upon years in a potentially exposed job was divided into low « 13 years) and high (?:.13 years) dose groups. 31 (5.4%) of the high dose vs.24 (4.1%) of the low dose group had ILO scores ?:. 1/0 indicating pulmonary fibrosis while 147 (25.7%) of the high dose group verses 121 (20.7%) of the low dose group have meet the case definition of pulmaonary fibrosis (spirometry combined with parenchymal disease) ($p < 0.05$). In a 2 x 4 table analysis (binary fibrosis x binary asbestos and radiation exposure) 90 (32.3%) in the high asbestos/ high radiation (> 20mSv deep dose) group met the cases definition for fibrosis vs. 81 (19.2%) in the low/low group ($p = 0.065$). A dose response was seen for fibrosis risk with increasing radiation at exposure rates around the occupational standard. CONCLUSIONS: Worker protection standards are based upon single exposures not accounting for the constellation of exposures frequently encountered. Deep dose external radiation may add to the fibrotic effect of asbestos in workers exposed to both toxicants.

Publications:

Takaro TK, Griffith WC, Omri K, Checkoway Hand Faustman EM. Asbestos and radiation as combined exposures in pulmonary fibrosis. Toxicologist N: 42.2003 (abstract).

Technical Report for Combined Effects of Radiation and Asbestos in Producing Pulmonary Fibrosis

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List of Abbreviations

CEDE	Committed Effective Dose Equivalent
COCS	Common Occupational Classification System
CRESP	Consortium for Risk Evaluation with Stakeholder Participation
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
ILO	International Labour Organization
IRB	Institutional Review Board
JEM	Job Exposure Matrix
LET	Linear Energy Transfer
NORA	National Occupational Research Agenda
POR	Prevalence Odds Ratio
PR	Prevalence Ratio
PSCR+	Personal Security Clearance Record
REMS	Radiation Exposure Monitoring
REX	Radiation Exposure System
REX	Radiological Exposure System
TNF*a*	Tumor Necrosis Factor alpha
WLM	Working Level Months

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Abstract

RATIONALE: Workers exposed to asbestos may encounter radiation as radon or from other sources. Both asbestos and radiation are etiologic agents in pulmonary fibrosis. The aim of this study is to determine whether concomitant radiation exposure in asbestos workers increases the incidence of pulmonary fibrosis.
METHODS: 2263 asbestos exposed former nuclear weapons workers from a medical surveillance program form the study cohort. PA chest radiographs and spirometry were performed for screening. Fibrosis was defined by B-read opacity profusion category on chest radiographs $\geq$ 1/0, or spirometric evidence of restrictive or mixed disease. The cohort is largely male (91.0%) with an average age of 63.3 years. 1157 workers had complete work histories, including external radiation badge doses and laboratory data.
RESULTS: The demographic and fibrosis endpoints were similar in the entire cohort vs. the 1157 analyzed. Asbestos exposure based upon years in a potentially exposed job was divided into low (< 13 years) and high ($\geq$13 years) dose groups. 31 (5.4%) of the high dose vs.24 (4.1%) of the low dose group had ILO scores $\geq$ 1/0 indicating pulmonary fibrosis while 147 (25.7%) of the high dose group verses 121 (20.7%) of the low dose group have meet the case definition of pulmaonary fibrosis (spirometry combined with parenchymal disease) ($p < 0.05$). In a 2 x 4 table analysis (binary fibrosis x binary asbestos and radiation exposure) 90 (32.3%) in the high asbestos/ high radiation (> 20mSv deep dose) group met the cases definition for fibrosis vs. 81 (19.2%) in the low/low group ($p = 0.065$). A dose response was seen for fibrosis risk with increasing radiation at exposure rates around the occupational standard.
CONCLUSIONS: Worker protection standards are based upon single exposures not accounting for the constellation of exposures frequently encountered. Deep dose external radiation may add to the fibrotic effect of asbestos in workers exposed to both toxicants.

Significant Findings

This study of 2263 asbestos exposed workers from USDOE's Hanford Nuclear Reservation supports the concept that radiation adds to the risk of pulmonary fibrosis due to asbestos fibers. Dichotomous analysis of fibrosis based upon four dose groups was not statistically significant, but collapsing the middle dose groups showed significance at the $p = 0.065$ level. As expected, age was co-linear with cumulative asbestos exposure in this study. When age was removed from the regression model that combined production worker and building trades workers high exposure group shows significantly more disease than the groups without combined high exposures.

Usefulness of the findings

The results could affect the current surveillance measures deployed for the hundreds of workers involved in the decontamination and destruction of 1940-60 era buildings around the nuclear weapons complex by lowering the threshold of surveillance for workers with both radiation and asbestos exposures. Additionally, the majority of the cohort is older than 60 years, with some receiving their significant exposures at older ages. This study assessed differential susceptibility based upon age to these two fibrinogenic agents and found a suggestion of increased effect at older ages. While it is unlikely that information from this study will impact primary prevention for these exposures, opportunities for secondary prevention through modifications of surveillance programs based on multiple exposures may possibly be influenced by these results.

Scientific Report

Background

Worker protection standards are based upon single exposures and do not account for the constellation of exposures frequently encountered by nuclear weapons production and site clean-up workers or by the growing number of hazardous waste workers. For example these workers may encounter asbestos fibers during buildings under going radiation decontamination and demolition and be concomitantly exposed to radiation. Both hazards cause pulmonary fibrosis. While personal protective equipment would usually be worn in current work situations involving these hazards, hazardous waste workers are not always aware of the exposure hazards when entering old and poorly characterized sites and they may not have deployed adequate protection in such settings in the past. Protection factors are generally based on exposure standards for individual agents rather than combined hazards. Older workers and retirees are most at risk for pulmonary fibrosis due to the increased cumulative exposures frequently seen in these workers over their work life, and the possible increased biological effect of exposures later in life. The purpose of this study is to determine whether ionizing radiation contributes to the fibrogenic effects of asbestos in workers at a former nuclear weapons facility.

Figure 1. Radioactively contaminated asbestos from Manhattan Project, 1994 USDOE, (1997) Linking Legacies (93).

Asbestos has been implicated in pulmonary fibrosis since the beginning of the twentieth century, well before its carcinogenic properties were noted in the last half of the century (1). Whereas the carcinogenic mechanisms of asbestos related lung cancer remain unknown, significant advances have been made in elucidating the mechanisms of fibrosis secondary to mineral and fiber particulates. Some investigators such as Mossman and Gee have postulated that a relationship must exist between the two diseases, with fibrosis a necessary precursor to asbestos induced lung cancer (15). Cullen, along with Case and Dufresne and others argue against such a relationship (16,17,18). The controversy regarding the relationship between these disease entities is likely to continue until the mechanisms of asbestos carcinogenicity and fibrotic lung disease are known.

The pathologic mechanisms leading to the fibrotic lung condition asbestosis appear to be due to inflammation at the site of fiber deposition in the lung. Alveolar macrophages are probably the most important mediator (19). This inflammatory response includes a shift in the macrophage phenotype towards the immune activator and away from suppressor macrophages (20), and a secretion of chemotactic and growth factors which promote fibroblast proliferation and adhesion, precursors to fibrosis (15,21,22). Pulmonary fibrosis also involves the production of cytokines, such as tumor necrosis factor alpha (TNF*a)*. This inflammatory polypeptide was found to be elevated in several studies of fibrosis, with particularly high levels in patients with asbestosis who develop lung cancer (23). Piquet and colleagues determined that TNF*a* is a prerequisite for the fibrotic process in silicosis (24).

Radiation induced pulmonary fibrosis has been demonstrated only in high dose exposures, such as therapeutic radiation to the chest (15-20 Gy). Inflammatory injury in the alveoli is followed by fibrosis (25,26). The mechanism is thought to be through direct damage to epithelial cells with some of the same pulmonary macrophage and cytokine involvement as noted in asbestosis. While radiation induced pulmonary fibrosis is generally not found at doses common in the occupational setting, no threshold for its fibrogenic effect has yet been established. Doses as low as 10 Gy have caused fibrosis in the clinical setting (27). Similar cellular mechanisms seem to be involved in the two fibrotic processes, but the degree of fidelity of these mechanisms is unknown. If the two processes are the same this study should show an additive effect. If the mechanisms are different a synergistic effect may be seen (1).

Occupational exposures to internally deposited radionuclides in the lung usually come from inhaled particles deposited in the lung and may produce either low-LET radiation or high-LET radiation depending upon the specific nuclide. The radiation comes from the radioactive decay of the nuclides contained in the particle. Radionuclides in particles may produce doses to the lung for decades after their original inhalation and deposition on the lung, depending on the chemical composition of the particles and the half-lives of the radionuclides.

The total number of workers at USDOE nuclear sites is not known. Currently, the ten largest sites employ over 60,000 workers, though some estimates are up to 120,000 when all sub-contractors are considered (2). In a March 1995 white paper, USDOE's Office of Health Studies (EH-6) referred to records on 600,000 former workers, and estimated that considering only building trades workers, throughout the nuclear complex, 31,000 workers were probably exposed to asbestos during their work history at DOE (3). Based on our information regarding asbestos exposure at Hanford, this is probably an underestimate of the total number of workers exposed. Hanford represents about 20-30% of the total DOE workforce over the 55 years existence of the weapons complex. We conservatively estimate 9,394 "probably" exposed to asbestos and an additional 24, 970 "possibly" exposed at that site alone (4) (Appendix H). Interim findings from the USDOE Former Worker Program supports the notion that these exposures were medically significant. With 11,611 workers examined, 2,461 (21.2%) have chest radiographs with ILO

classifications consistent with asbestos related disease, and 3,414 (29.4%) have spirometry consistent with pulmonary fibrosis (restrictive or mixed disease) (94).

Specific Aims:

The accomplishments of the project were significantly effected by the inability to obtain the internal dosimetry anticipated. This was due to restricted funding at a crucial juncture of the project after over two years of negotiations with the Pacific Northwest National Laboratory, which houses the dosimetry data. The Consortium for Risk Evaluation with Stakeholder Participation (CRESP) was undergoing significant turmoil in funding from USDOE at the time negotiations were completed and could not commit the funds necessary to transfer the data. Hence, the estimates of doses relied upon external dosimetry already in possession of the Former Worker Projects. While Aims 1 and 2 could still be accomplished, Aims 3 and 4 required the comparison of internal dose estimates and could not be accomplished without this data. It is important to note that particularly for building trades workers many workers in the cohort did not have even external radiation doses (74%) as shown in Table 2.

Aim 1. Determine whether concomitant radiation exposure increases the risk of pulmonary fibrosis as demonstrated by an increase in ILO opacity profusion category on chest radiographs, or spirometry based case definitions of pulmonary fibrosis.

This was accomplished using external dosimetry as the estimate for radiation dose.

Aim 2. Using dates of first exposure to asbestos and radiation determine whether workers with radiation and asbestos exposures later in life are at greater risk for pulmonary fibrosis than workers exposed at a younger age based upon an increase in ILO opacity profusion category on chest radiographs, or spirometry based case definitions of pulmonary fibrosis.

This was accomplished using external dosimetry as the estimate for radiation dose.

Aim 3. Determine the relative importance of external gamma radiation vs. calculated internal lung dose using whole body counting and urinary bioassay on ILO profusion score in this population exposed to asbestos.

This was not accomplished for the reasons outlined above.

Aim 4. Determine the relative effect of low Linear Energy Transfer (LET) vs. high LET radiation in the risk of developing fibrotic disease and any difference in time course of this response.

This was not accomplished for the reasons outlined above

Methods:

Cohort:
The University of Washington Hanford Former Worker Medical Monitoring Program identified 9,394 Hanford production workers with probable asbestos exposure based on decade of work and job titles as part of a 1996 needs assessment (5). In a similar needs assessment, the Center to Protect Workers Rights estimated that 30,000 workers may have been at risk from occupational exposures including asbestos. The job exposure matrix (JEM) used by the University of Washington Hanford Former Worker Medical Monitoring Program identified 11,460 building

trades workers, with over 2,550 estimated to have probable asbestos exposure and an additional 19,608 with possible exposure (4). Identification of the population required combining multiple databases. Each of the databases used is described below:

Flow Gemini is the Hanford Environmental Health Foundation medical examination and scheduling system. It contains 47,604 workers who have been scheduled for examinations since 1985. Flow Gemini contains medical information and limited demographic information from the Hanford PeopleCore and HSS systems.

REMS is the central repository for Radiation Exposure Monitoring (REMS) at DOE-HQ. It contains 42,874 Hanford workers who have been gathered from the REX Radiological Exposure System. The records cover the years 1985 to 1996. REMS contains very limited demographic information (i.e., birth year rather than birth date, first initial often instead of first name) and annual dose records. The dose records also have a job code associated with them, but not every exposure corresponds to a person, and not every person has an exposure. Building or job location is not recorded in REMS. Internal dose records were calculated using Annual Effective Dose Equivalent prior to 1985-1993, and Committed Effective Dose Equivalent thereafter.

OHH88 is the source file for the employment history data used to create the cohort for Ethel Gilbert's 1989 mortality study of workers who began working between 1945 and 1986. Data include personal identifiers, date and place of birth, death year, gender, race, work history dates, job title text, and 1971 Bureau of Census job code. All workers have at least one job code and only 0.1% of the workers have no beginning date for their work history while 14.3% have no ending date.

The Radiological Exposure System (REX) maintains and reports individual Hanford worker, subcontractor and visitor radiological records since 1944 (except for some early Westinghouse employees). It is held by Batelle Pacific Northwest National Laboratories. REX contains internal dosimetry records, radiation badge readings, and limited demographic information. Unfortunately, internal dosimetry has not yet been received. The deep dose radiation data based upon external personal dosimeters for the asbestos exposed cohort targeted for this investigation is shown in
Table 3.

PSCR+ (Personal Security Clearance Record) is the Hanford security badging system, formerly held by B & W Protec, Inc. Complete records only go back to 1985 (since the inception of the Central Badging Office). Prior to 1985, each company maintained their own internal badging systems, and the quality and quantity of data dumped into PSCR+ is unknown. There are approximately 100,000 workers, subcontractors and visitors in the system. Some small number never worked at Hanford.

Exposure:
As is generally the case, retrospective estimation of exposures for individual workers has been challenging. For the former Hanford workers to date, in order to estimate exposures we have: 1) reviewed documents describing hazards on site, 2) created a job exposure matrix, 3) collected questionnaire data and 4) accessed the Radiation Exposure System (REX) and REMS databases. The complete JEM is demonstrated and described in detail in the October Former Hanford Worker Needs Assessment, Version 1.1 (5). Briefly, the 73 existing Common Occupational Classification System (COCS) Codes developed by the DOE were examined by our four industrial hygienists and grouped within the more broad COCS categories resulting in the development of 42 distinct occupational exposure categories. Each of the occupational exposure

categories represents a group of job categories likely to have been exposed to the same hazards at Hanford. A job-exposure matrix was then constructed such that an estimate of exposure could be assigned for each of the 42 hazards to each occupational category for each of five decades (1943-1990) of Hanford operations. A group of four certified industrial hygienists was assembled to develop estimates for the qualitative exposure estimates of the matrix. Exposure categories were: "probably not exposed" (0), "possibly exposed depending on location and specific tasks" (1), and "probably exposed" (2). Adding the 13,050 new individuals from REX who have job title information gives 4,378 additional workers to JEM for a total of 82,771 individuals.

From the population identified by these databases and those identified through outreach efforts, 1418 building trades workers and 845 production workers with potential asbestos exposure had availed themselves to an examination as of July 1, 2003. The examination included spirometry and chest radiograph with B-read. A total of 2263 workers were examined and included in the initial cohort (Table 1).

Asbestos exposure was estimated in the following manner. For production worker asbestos exposure was taken from the job history questionnaire completed by the worker. Years in a potentially exposed job were summed (high > 13 yrs in trade, low < 13 yrs in trade). For building trades workers, asbestos exposure was taken from an interviewer administered questionnaire with job history derived from the question, "how often did you work with asbestos" (high = often, regularly) (low = sometimes, rarely, hardly ever). Years at Hanford were also calculated, but this did not appear to be reflective of time in high risk job. These categories were defined to enable approximately equal numbers in each asbestos exposure category.

788 production workers and 369 building trades workers had adequate asbestos and radiation exposure information. Of the 1,049 Building Trades workers with medical exams and asbestos exposure, 864 have no dose (deep or shallow) in the record. 135 have '0' for deep dose and '0' for shallow dose 50 have '0' for deep dose and have a shallow dose. We chose not to include individuals with incomplete records due to missing exposure data. When available, external radiation dose was determined by badge dosimetry recorded in either the REX or REMS databases obtained from the Pacific Northwest National Laboratory as Deep Dose and Shallow Dose. Neutron dose was not used in this analysis due to the limited amount of complete data. For production workers, annual average exposure computed as deep or shallow dose/ years in radiation exposed job. When missing dates in radiation exposed job(s) was encountered, deep or shallow dose for years worked at Hanford was used. The duration of the production worker radiation exposure was estimated by job history as a sum of years in potentially exposed job(s). If dates were missing in radiation exposed job(s), the sum of years worked at Hanford was used.

The last year employed in a radiation exposed job was determined from the job history. If dates for last radiation exposed job was missing, last year worked at Hanford was used. For building trades workers annual average exposure was computed as deep or shallow dose for total years worked at Hanford. Years worked at Hanford for this group may be over estimated due to the practice of building trades workers to rotate to jobs off site and return, increasing the chances that start and stop dates will be missed. For this group no job history specific to radiation exposure was available. Smoking information was collected for both groups by questionnaire, administered by an interviewer for the building trades workers and self-administered for the production workers.

Case definition:
1) ILO Profusion score ≥ 1/0, or
2) restrictive disease on spirogram defined by FVC < 95% C.I. and FEV1/FVC > 95% C.I. using predicted values from Crapo (84), or
3) mixed obstructive and restrictive disease on spirogram defined by by FVC < 95% C.I. and FEV1/FVC < 95% C.I. using predicted values from Crapo (84). The spirometric classification scheme is adopted from the CARET trial (54).

Dichotomous radiation dose categories were established for Deep and shallow doses as follows:
Deep dose: high ≥ 20 mSv. Low < 20 mSv,
Shallow dose: high ≥ 5 mSv. Low < 5 mSv.

Analysis was performed using SPSS (92) Descriptive statistics utilizing t-test for continuous variables and chi-square for categorical variables were used. Logistic regression was performed using age, pack-years, exposure categories and radiation exposures for individuals >45 years of age prior to 1970 were used in various models. Pearson correlation coefficients were evaluated for cumulative exposure and age. Based upon the recommendations of Blanc, the data were also modeled with age removed to evaluate the effect of co-linearity with age and years of asbestos exposure (96).

Results:

The 2263 asbestos exposed former Hanford workers are predominantly male, (93.6%), particularly for the building trades workers (98.4%). 85.3% of the production workers are male. The average age of the cohort is 63.3 years. Of the 1157 with adequate exposure information to be included in the final analysis 91.0% are male, and the average age is not significantly different from the larger cohort. Additionally, no significant differences between the complete cohort and the subset available for analysis are found for the key variables of profusion score, restrictive or mixed disease, fibrosis case, pleural plaque or pack-years (Table 1).

For the 1157 workers in the final analysis, 93.1 % are white, 1.5% African American, Asian and Hispanic, respectively. The average number of years worked at Hanford is 20.19 (s.d. 13.29). There is no significant difference between building trades and production workers in years worked at Hanford (Table 2).

For the building trades workers, the subset of workers with radiation data are younger and have fewer pack-years of smoking and less fibrosis and pleural plaque than the other asbestos exposed building trades workers. For the production workers, a much larger proportion of the asbestos exposed population have radiation data (93.2 % vs. 26.0%), and there are no significant differences in these baseline characteristics (Table 3) or prevalence of fibrosis.

Table 4 describes the analytical cohort by low and high asbestos category. The high exposure group is significantly older, have more years at Hanford, more pack-years and more fibrosis by case definition. As shown in Table 5, production workers with > 13 years in an asbestos exposed job are also older and show significantly higher ILO profusion scores, evidence for restrictive lung disease, pulmonary fibrosis (by case definition) and pack-years than those in asbestos exposed jobs for 13 or fewer years. Pleural plaque and mixed obstructive and restrictive disease is not significantly higher in the higher exposure group. For the 369 building trades workers included in the radiation and asbestos cohort, no significant differences are noted between the high and low exposure groups for age, smoking or any of the disease endpoints.

Tables 6a-f describe the analytic cohort by high asbestos/high radiation, high asbestos/ low radiation, low asbestos/high radiation and low asbestos/ low radiation exposure categories for both deep and shallow dose. Rows show dichotomous classification for the presence or absence of pulmonary fibrosis by the case definition. For the combined cohort deep dose, in the high asbestos/high radiation the difference in the proportion with fibrosis between the 4 groups are not significant ($p= 0.137$). If middle groups are collapsed (high asbestos/ low radiation, low asbestos/high radiation) the difference approaches statistical significance ($p= 0.065$) with the high/high group demonstrating more fibrosis than the other two groups.

Various models were produced using logistic regression to evaluate the role of age, pack-years (continuous), exposure categories as described in Tables 6, asbestos and radiation exposure categories, age ≥ 45 in 1970 (reflective of greater dose at later age) for shallow and deep radiation doses. Only age and pack-years reach statistical significance ($\beta = 0.056$, $p = 0.0001$ and $\beta = 0.017$, $p = 0.0001$ respectively) . For the high radiation/high asbestos category $\beta = 0.205$, $p = 0.283$. The same was true for shallow dose, the high radiation/high asbestos effect was not seen ($\beta = 0.015$, $p = 0.943$).

Figure 2 describes the impact of age and smoking on fibrosis. Older heavier smokers demonstrate more fibrosis except in the oldest age group. Up through age 70 age appears to have a greater impact on fibrosis than smoking. Co-linearity between age and cumulative exposure and pack-years and cumulative exposure were investigated and shown to be significantly related with Pearson correlation co-efficients of 0.376 for high radiation/high asbestos and - 0.274 for low radiation/ low asbestos ($p= 0.000$). Pack-years was also slightly correlated ($R= 0.150$ for high radiation/high asbestos) and it was correlated with age ($R= 0.244$). If age is removed from the exposure model as recommended by Blanc (95) due to co-linearity with cumulative exposure, combined exposures in the high radiation/high asbestos category does confer additional risk for fibrosis when compared to the other combined dose groups. Also demonstrated is that the risk of fibrosis due to smoking is relatively small compared with that for asbestos and radiation exposure with an O.R. 1.83 for the high radiation/high asbestos (95%CI 1.25, 2.66) vs. 1.02 (95%CI 1.013, 1.026) for smoking. The two high/low categories do not confer risk. That deep dose radiation plays a role in this risk for high radiation/high asbestos is suggested by a dose response for fibrosis seen when dividing radiation deep dose into 0.2-10 mSv, 10-100 mSv and > 100 mSv categories as shown in Table 7.

To further investigate the role of age in pulmonary fibrosis we repeated the logistic regression using the portion of the cohort 60 years old or younger. For the 420 workers in this group, neither age, pack-years or exposure categories were significant predictors of risk for the 61 cases of pulmonary fibrosis. Likewise in the sub-cohort exposure to asbestos and radiation did not significantly contribute to the incidence of pulmonary fibrosis.

Figure 3 demonstrates the years of greatest internal radiation deposition. This corresponds with years of highest external dose used here. To address Aim 2 hypothesizing that workers exposed later in life have a greater fibrogenic effects from radiation we compared workers who were ≥ 45 years old in 1970 when doses were highest, to those younger than 45 in that year. Though not reaching statistical significance in the logistic regression model, the effect was in the opposite direction, i.e. workers who were younger than 45 in 1970 showed greater effect. When restricting the model to age and age ≥ 45 years old in 1970, radiation exposure for those ≥ 45 years old in 1970 suggested a protective effect for fibrosis (O.R. 0.51, 95% CI 0.31-0.84)

Discussion:

This study of 2263 asbestos exposed workers from USDOE's Hanford Nuclear Reservation supports the concept that radiation adds to the risk of pulmonary fibrosis due to asbestos fibers. Dichotomous analysis of fibrosis based upon four dose groups was not statistically significant, but collapsing the middle dose groups showed significance at the p= 0.065 level. These collapsed categories represent mixed low and high dose groups justifying their consolidation. As expected, age was co-linear with cumulative asbestos exposure in this study, and it is only when age was removed from the regression model that the combined high exposure group shows significantly more disease than the groups without combined high exposures.

As noted by Blanc in his meta-analysis in 1991, significant co-linearity often exists between cumulative exposures such as asbestos and age or pack-years using combined data-sets with using 2,939 asbestos exposed workers with B-read chest radiographs and simulating various cumulative years of asbestos exposures (95). Such a relationship between age and cumulative asbestos exposure was indeed demonstrated in this study. While age and pack-years appear to confer risk for fibrosis, when age is removed from the models the combined exposures of radiation and asbestos become highly significant. Our age restricted analysis with 61 cases of fibrosis, suggested that age is not likely to contribute to pulmonary fibrosis risk at least before the age of 60. That deep dose radiation contributes to the fibrosis risk is supported by findings of a dose response seen when terciles of exposure with this measure are used. Age at time of exposure does not appear to affect the risk of pulmonary fibrosis.

For most workers, particularly those in production jobs, radiation dose is more accurately quantified than asbestos dose because of the badge dosimetry records for radiation. Industrial hygiene measures for asbestos exposure are essentially non-existent for this cohort. Risk of fibrosis appears to increase with increasing work-life doses, at levels near the current annual occupational standard of 50 mSv., adding to the credence of a combined effect. The analysis of radiation dose would be improved by the inclusion of internal deposition and calculated lung dose, but strong correlations between external dose as collected here and internal dose has been demonstrated by others (96).

For the building trades asbestos cohort, the differences between the entire cohort and those with data for both radiation and asbestos are highly significant. This can be attributed to the fact that building trades workers had less monitoring performed in the early years at Hanford. Considering the subsequent findings in the study, the difference in fibrosis between the larger cohort and that with adequate radiation data is likely due to the significantly younger age of the radiation exposure subset for the building trades workers. Building trades workers in the high asbestos exposure category were the same age as the lower exposed group and did not show significantly increased evidence for fibrosis. Because older workers generally have more cumulative years of workplace exposure, misclassification for asbestos exposure is likely in this group. Non-Hanford asbestos exposure was not well characterized in this study, but is quite likely, particularly for the transient building trades. The studies conclusions are not changed appreciably with analysis restricted to production workers alone though confidence intervals are generally narrower with this restriction.

The pulmonary abnormalities reported here are confounded to some extent by cigarette smoking. The degree to which cigarette smoking contributes to increased profusion scores is controversial. Several investigators find that the ILO score increases by about one minor ILO category when smoking is added to asbestos (76,77); others found a larger effect with combined exposure and a small effect in non-exposed smokers (78). Finally, a few have found no increase in profusion

scores when smoking is an added exposure to asbestos (55,79). Restrictive disease is likely to be influenced similarly by smoking while mixed restrictive and obstructive disease will be more affected by smoking due to the well documented effect on air flow obstruction by cigarette smoke. In this study, pack-years contributed minimally to the risk of fibrosis and was correlated with age except for workers > 80 years of age. The dramatic drop off in fibrosis in the heaviest smokers in this oldest age group may be due to increased mortality in this group. The study would be considerably stronger were information on mortality related to respiratory disease available for all age groups. No such information is available for this cohort.

The results presented here demonstrate the importance of medical surveillance for asbestos related disease for the hundreds of workers involved in the decontamination and destruction of 1940-60 era buildings around the nuclear weapons complex. The threshold for surveillance for workers with both radiation and asbestos exposures should be low. Additionally, the majority of the cohort is older than 60 years, with some receiving their significant exposures at older ages. This study assessed differential susceptibility based upon age to these two fibrogenic agents and found increased fibrosis rates at older ages. While it is unlikely that information from this study will impact primary prevention for these exposures because protective measures are largely in place, opportunities for secondary prevention through modifications of surveillance programs based on multiple exposures could be influenced by these results.

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Table 1. Population descriptions

	Population of 2263 Asbestos Exposed			Subset of 1157 with Exposure Data		
	Production (n=845)	**Building Trades (n=1418)**	**Total (n=2263)**	**Production (n=788)**	**Building Trades (n=369)**	**Total (n=1157)**
Average Age	62.85	63.59	63.31	63.56	57.26	61.55
Profusion > 0/1	47 (5.6%)	65 (4.6%)	112 (4.9%)	44 (5.6%)	11 (3.0%)	55 (4.8%)
Restrictive Dz.	143 (16.9%)	132 (9.3%)	275 (12.2%)	136 (17.3%)	18 (4.9%)	154 (13.3%)
Mixed Dz.	64 (7.6%)	118 (8.3%)	182 (8.0%)	58 (7.4%)	20 (5.4%)	78 (6.7%)
Fibrosis (case definition)	238 (28.2%)	296 (20.9%)	534 (23.6%)	222 (28.2%)	46 (12.5%)	268 (23.2%)
Pleural Plaque	251 (29.7%)	454 (32.0%)	705 (31.2%)	240 (30.5%)	83 (22.5%)	323 (27.9%)
Packyears	18.64	15.71	16.79	18.73	12.03	16.56

No differences significant at p = 0.05 level between complete population and subset

Table 2. Demographics Data

	Combined	**Production workers**	**Construction worker**
Average	61.55 (11.16 s.d.)	63.56 (11.44 s.d.)	57.26 (9.17 s.d.)
race	White 93.1 % Black 1.5% Asian 1.5% Hispanic 1.5% Indian/AK. Native 0.7% Pacific Islander 0.3% Other 0.5%	White 94.0% Black 1.8% Asian 0.3% Hispanic 2.2% Indian/AK. Native 0.4% Pacific Islander 0% Other 0.8%	White 91.3% Black 0.8% Asian 4.1% Hispanic 0% Indian/Alaskan Native 1.4% Pacific Islander 1.1% Other 0%
gender	Male 91.0% Female 9.0%	Male 87.8% Female 12.2%	Male 97.8% Female 2.2%
Ave # Years at Hanford	20.19 (13.29 s.d.)	19.07 (13.94 s.d.)	21.71 (9.10 s.d.)

Table 3. Tests for individual population differences (Production and Building Trades)

	Production Worker Data			Building Trades Data	
	asbestos exposed (n=845)	Radiation subset (n=788)		asbestos exposed (n=1418)	Radiation subset (n=369)
Average Age	62.85	63.56	Average Age*	63.59	57.26
Profusion ≥ 1/0	47 (5.6%)	44 (5.6%)	Profusion ≥ 1/0	65 (4.6%)	11 (3.0%)
Restrictive Dz.	143 (16.9%)	136 (17.3%)	Restrictive Dz.*	132 (9.3%)	18 (4.9%)
Mixed Dz.	64 (7.6%)	58 (7.4%)	Mixed Dz.	118 (8.3%)	20 (5.4%)
Fibrosis (case definition)	238 (28.2%)	222 (28.2%)	Fibrosis* (case definition)	296 (20.9%)	46 (12.5%)
Pleural Plaque	251 (29.7%)	240 (30.5%)	Pleural Plaque*	454 (32.0%)	83 (22.5%)
Packyears	18.64	18.73	Packyears*	15.71	12.03

* $p < 0.05$ (t-test)

Table 4. Comparison of combined production and building trades asbestos exposure groups (high vs. low) for combined programs

	Low Exp (n=585)	**High Exp (n=572)**
Age*	58.79	64.37
Profusion > 0/1	24 (4.1%)	31 (5.4%)
Restrictive dz.	69 (11.8%)	85 (14.9%)
Mixed dz.	38 (6.5%)	40 (7.0%)
Fibrosis*	121 (20.7%)	147 (25.7%)
Pleural plaque	157 (26.8%)	166 (29.0%)
Packyears*	14.23	18.87
Yrs at Hanford*	13.36	26.63

*** p< 0.05 (t-test)**

Table 5. Comparison of asbestos exposure groups (high vs. low)

	Production Worker Data			**Building Trades Data**	
	Low Exp (n=403)	**High Exp (n=385)**		**Low Exp (n=182)**	**High Exp (n=187)**
Age*	59.28	68.04	**Age**	57.51	56.82
Profusion > 0/1	18 (4.5%)	26 (6.8%)	**Profusion > 0/1**	6 (3.3%)	5 (2.7%)
Restrictive dz.*	59 (14.6%)	77 (20.0%)	**Restrictive dz.**	10 (5.5%)	8 (4.3%)
Mixed dz.	26 (6.5%)	32 (8.3%)	**Mixed dz.**	12 (6.6%)	8 (4.3%)
Fibrosis*	95 (23.6%)	127 (33.0%)	**Fibrosis**	26 (14.3%)	20 (10.7%)
Pleural plaque	111 (27.5%)	129 (33.5%)	**Pleural plaque**	46 (25.3%)	37 (19.8%)
Packyears*	15.80	21.68	**Packyears**	10.93	13.11

*** p< 0.05 (t-test)** *** p< 0.05 (t-test)**

Table 6 A-F. Asbestos/Radiation Tables
6. A-B. Production (Deep Dose & Shallow Dose)
6. C-D. Building Trades (Deep Dose & Shallow Dose)
6. E-F. Combined (Deep Dose & Shallow Dose)

Table 6 A. Production Deep Dose

Fibrosis	High rad. & high asb* (n=272)	High rad. & low asb (n=153)	Low rad. & high asb (n=113)	Low rad. & low asb* (n=250)
No	183 (67.3%)	116 (75.8%)	75 (66.4%)	192 (76.8%)
Yes	89 (32.7%)	37 (24.2%)	38 (33.6%)	58 (23.2%)

***p<0.05 (using chi-square test comparing fibrosis in this category to all others)**

Table 6 B. Production Shallow dose table

Fibrosis	High rad. & high asb* (n=272)	High rad. & low asb* (n=280)	Low rad. & high asb (n=36) (p=.481)	Low rad. & low asb (n=123) (p=.718)
No	234 (67.0%)	218 (77.9%)	24 (66.7%)	90 (73.2%)
Yes	115 (33.0%)	62 (22.1%)	12 (33.3%)	33 (26.8%)

***p<0.05 (using chi-square test comparing fibrosis in this category to all others)**

Table 6 C. Building Trades Deep Dose

Deep dose table

Fibrosis	High rad. & high asb* (n=50)	High rad. & low asb (n=10) (p=.089)	Low rad. & high asb (n=180) (p=.278)	Low rad. & low asb (n=172) (p=.623)
No	6 (85.7%)	7 (70.0%)	161 (89.4%)	149 (86.6%)
Yes	1 (14.3%)	3 (30.0%)	19 (10.6%)	23 (13.4%)

***p<0.05 (using chi-square test comparing fibrosis in this category to all others)**

Table 6 D. Building Trades Shallow dose

Fibrosis	High rad. & high asb (n=50)	High rad. & low asb (n=54)	Low rad. & high asb (n=137)	Low rad. & low asb* (n=128)
No	42 (84.0%)	50 (92.6%)	125 (91.2%)	106 (82.8%)
Yes	8 (16.0%)	4 (7.4%)	12 (8.8%)	22 (17.2%)

***p<0.05 (using chi-square test comparing fibrosis in this category to all others)**

Table 6 E. Combined Programs Deep Dose

Fibrosis	High rad. & high asb* (n=279)	High rad. & low asb (n=163)	Low rad. & high asb (n=293)	Low rad. & low asb* (n=422)
No	189 (67.7%)	123 (75.5%)	236 (80.5%)	341 (80.8%)
Yes	90 (32.3%)	40 (24.5%)	57 (19.5%)	81 (19.2%)

***p<0.05 (using chi-square test comparing fibrosis in this category to all others)**

Table 6 F. Combined Programs Shallow dose table

Fibrosis	High rad. & high asb* (n=399)	High rad. & low asb (n=334)	Low rad. & high asb* (n=173)	Low rad. & low asb (n=251)
No	276 (69.2%)	268 (80.2%)	149 (86.1%)	196 (78.1%)
Yes	123 (30.8%)	66 (19.8%)	24 (13.9%)	55 (21.9%)

***p<0.05 (using chi-square test comparing fibrosis in this category to all others)**

Table 7. Radiation dose category and risk of pulmonary fibrosis

Deep dose	Odds Ratio	95% Confidence interval
0.2- 10 mSv	0.97	0.612-1.54
>10-100 mSv	1.51	1.03-2.22
>100 mSv	1.89	1.20-2.97

Figure 2. Smoking pack-years by age group

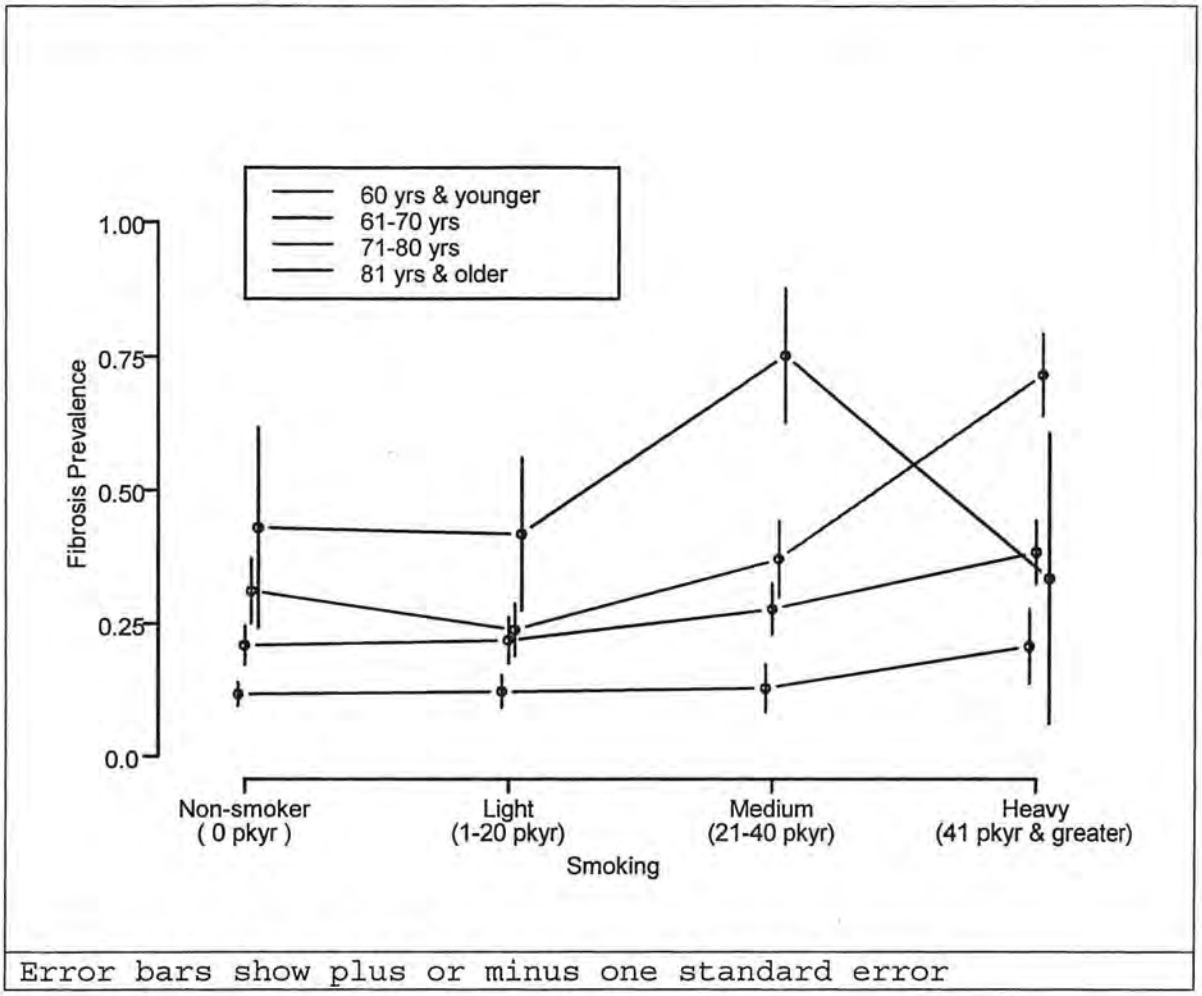
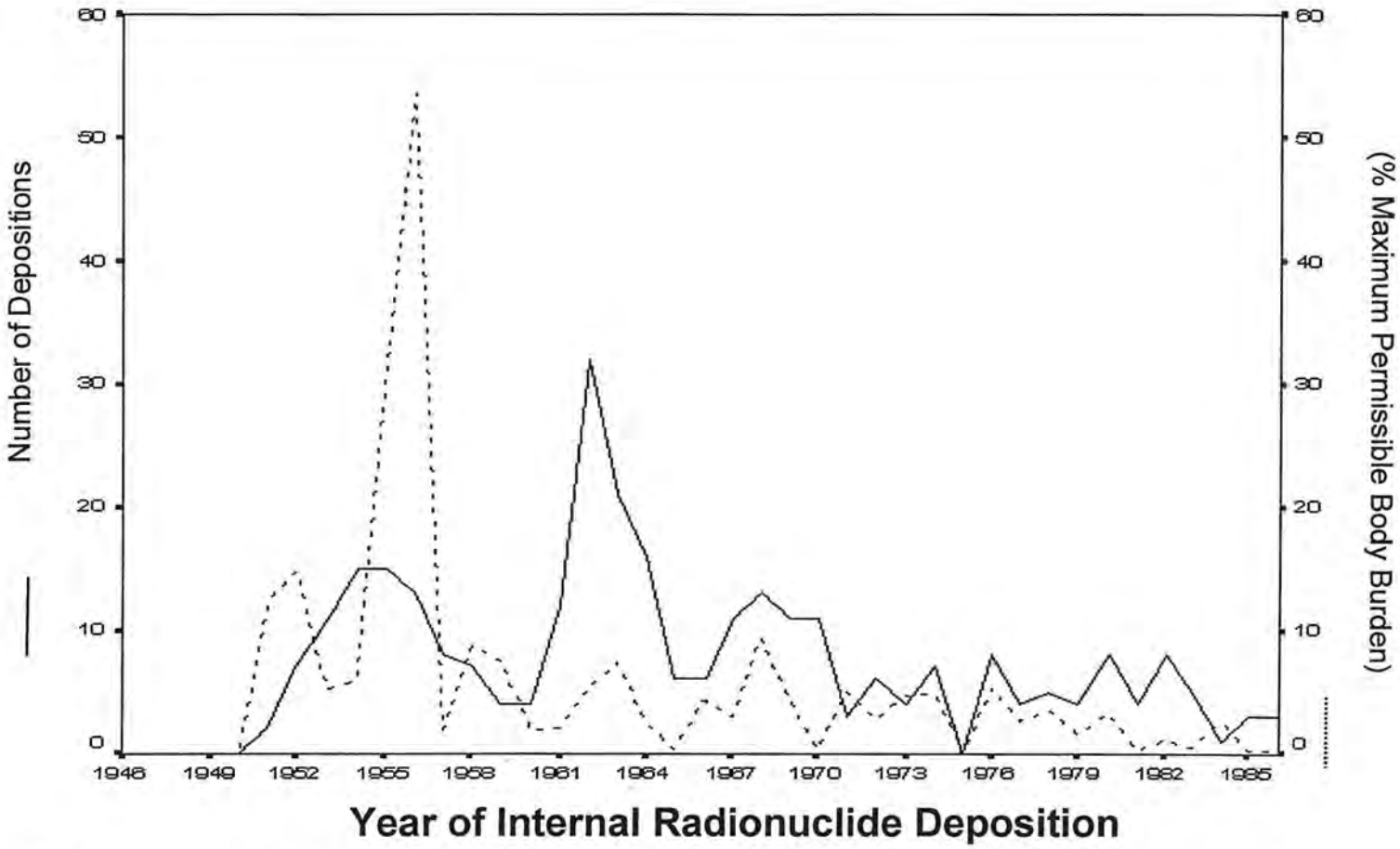


Figure 3. Data from Hanford Section of Comprehensive Epidemiologic Repository (CEDR) For Internal Depositions



MPBB was an administrative assignment, and calculations changed over time as understanding of radionuclide absorption improved.
In 1989, the Maximum Permissible Body Burden for Pu-238, 239 and 240 were 40 nano-curies, and 900 nano-curies for Pu-241.

Publications

Takaro TK, Griffith WC, Omri K, Checkoway H and Faustman EM. Asbestos and radiation as combined exposures in pulmonary fibrosis. Toxicologist 72: 42. 2003 (abstract).

Publication planned for submission to Radiation Research or Health Physics based upon the above abstract.

Presentations and Posters

Takaro TK, Griffith WC, Omri K and Checkoway H. Asbestos and radiation as combined exposures in pulmonary fibrosis. Asbestos Research conference, University of Montana, Missoula, MT. June 2002 (presentation).

Takaro TK, Griffith WC, Omri K and Checkoway H. Asbestos and radiation as combined exposures in pulmonary fibrosis. Am. Thoracic Soc. Annual Meeting 2003 (poster).

Shack, Stephanie

From: Tim Takaro [ttakaro@u.washington.edu]
Sent: Thursday, December 04, 2003 8:16 PM
To: Columbia, John R.
Cc: Shack, Stephanie
Subject: Re: K01 OH00181

Greetings!
Attached is the end of project report for K01-OH00181.
Thanks for your patience.
-Tim

Tim K. Takaro, MD, MPH
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University of Washington
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characterized and studied for chemokine and cytokine mRNA expression by in situ hybridization. In vitro antigen enhancement of MCP-1 will be compared by ANOVA for associations with MCP-1 and cytokine levels in BAL fluid. Once validated as a diagnostic biomarker, the MCP-1 assay can be utilized as a diagnostic method for differentiating workers suspected of DA from those with non-DA or from those individuals with non-occupational asthma.
Program Area: Asthma & COPD

Title: Combined Effects of Radiation and Asbestos in Producing Pulmonary Fibrosis
Grant Number: 5 K01 OH000181-03
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Description: The main focus of this study is to determine whether concomitant radiation exposure increases the fibrogenic effect of asbestos as demonstrated by an increase in ILO opacity profusion category on chest radiographs, or spirometry based case definitions of pulmonary fibrosis. Using a cohort design, 500 asbestos exposed nuclear workers will be divided into very low and high radiation dose groups based upon personal dosimetry records and then compared for evidence and degree of pulmonary fibrosis. The following hypotheses will be addressed: (1) Radiation dose increases the risk of pulmonary fibrosis in workers exposed to asbestos. (2) Exposures at ages greater than 45 years confer a greater risk than exposures at earlier ages. (3) Internal lung dose estimates are a better predictor of pulmonary fibrosis effect than external film badge dosimetry. (4) Chronic Low Energy Transfer (LET) radiation is more effective than brief exposures to high energy radiation in enhancing the fibrotic effects of asbestos. Answers to these questions should improve the risk profiling of former USDOE workers as well as those involved in future remediation of radiation and asbestos contaminated sites.
Program Area: Mixed Exposures