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43802 Health Effects of Occupational Exposures In PGDP Workers
David J. Tollerud, MD, MPH (P1)

Principal Investigator:
David J. Tollerud MD, MPH
Department of Environmental & Occupational Health Sciences
School of Public Health & Information Sciences
University of Louisville
Louisville, KY 40292
502-852-3007
david.tollerud@louisville.edu

Affiliation:
University of Louisville Research Foundation
Jouett Hall, Belknap Campus
Louisville, KY 40292

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Key Personnel

University of Louisville

David Tollerud, MD, MPH W.
Paul McKinney, MD Susan
Muldoon, PhD, MPH Robert
Jacobs, PhD
Irma Ramos, MD
Teresa Hughes, PhD
Nancy Reinhart, MPH
M. Caroline Chan, MPH

University of Cincinnati/
Cincinnati Children's Medical Center

Richard Hornung, DrPH, Consortium P1
Carol Rice, PhD
David Brewer, BS
Mona Ho, MS

University of Kentucky

Gail Brion, PhD, Consortium P1
Timothy Aldrich, PhD, MPH
Lawrence Figg, PhD
Kenneth Silver, SM, DSc Debra
Bahr, DrPH, MHA, RPh
Samantha Freitas, DrPH
Hege Ravdal, MA
Pavithra Damara
Ilva Iriate
Daniel Saman

Tricord

Steve Meiners
Kenneth Eger, PhD

TABLE OF CONTENTS

LIST OF TERMS AND ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
BJC	Bechtel Jacobs Corporation
DOE	Department of Energy
HWE	Healthy Worker Effect
ICD	International Classification of Diseases
JEM	Job Exposure Matrix
LTAS	Life Table Analysis Software
NDI	National Death Index
NIOSH	National Institute of Occupational Safety and Health
ORAU	Oak Ridge Associated Universities
PACE	Paper, Allied-Industrial, Chemical, and Energy
PGDP	Paducah Gaseous Diffusion Plant
PYAR	Person Years at Risk
SMR	Standardized Mortality Ratio
SRR	Standardized Rate Ratio
SSA	Social Security Administration
TMI	Three Mile Island
USEC	United States Energy Corporation

ABSTRACT

The purpose of this study is to address the concerns about potential health effects of Paducah Gaseous Diffusion Plant (PGDP) workers from current and past exposures. A synopsis of these aims will be discussed below.

The aims of this study can be summarized as follows:

- *develop a complete roster of past and present* employees at *the PGDP*
- *obtain copies of all electronic and hard copy files containing necessary exposure and personnel information*
- *develop a comprehensive list of jobs and job histories*
- *create a Job Exposure Matrix for chemical and radiation exposures*
- *link the Work History data with the Job Exposure Matrix*
- *evaluate worker Mortality for relationships with workplace exposures*
- *communicate the study results to employees and management*

The study team has succeeded in accomplishing the goals of the study. We have identified and collected what we believe to be essentially all available data for personal radiation exposure, area radiation measures, and relevant information on the chemical exposures of interest at the plant. We have completed a comprehensive mortality inventory of nearly all workers in our worker roster and have collected or requested death certificates or electronic death data identifying cause of death for all deceased workers. We have developed a complete roster of PGDP workers that represents a non-duplicative list of individuals that are found on one or more of the above roster lists. USEC has provided a detailed index of personnel record locations; these have been explored on a case by-case basis to complete full occupational intervals and job activities. We have completed a list of job descriptions and have obtained job histories on all workers from the plant opening to 1993, and on many workers through 2004. We have developed the job exposure matrix (JEM) database and have collected all known personal radiation and chemical exposure data. We have run pilot studies using actual exposure data and are completing the analysis of exposure patterns by job category. We have collected final mortality data and have run numerous analyses using the NIOSH life table statistical software. We have run standardized mortality ratio analysis to evaluate the distribution of causes of mortality in this cohort compared to the general US population. We are completing the final mortality analyses for chemical exposures and are developing the statistical models for analysis of personal radiation exposure and mortality. We have worked on developing communication strategies and have met with both management and employee groups to update them on the status of the project. NIOSH personnel will be working with us to develop and present the worker notification presentations. The PI will travel to Paducah to present the results to employees and management and answer questions they may have.

Final analyses and manuscript submissions are in progress, and copies of all manuscripts will be provided to NIOSH as they are accepted for publication. In general, the results confirm a strong healthy worker effect. The study also provides support for the relationship between radiation exposure and hematopoietic cancers that are consistent with previous studies. Increased rates of Alzheimer's deaths were found for some job titles, probably attributable to the strong healthy worker effect. There was some suggestion of a relationship between trichloroethylene exposure and non-Hodgkin's lymphoma, and between metals exposure, specifically arsenic, and risk of suicide. Several methodological analyses also explored the Paducah data.

SECTION 1

HIGHLIGHTS/SIGIN1FICANT FINDINGS

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TRANSLATION OF FINDINGS

The "healthy worker effect" is an observation often seen in occupational studies, where comparisons of diseases in workers to the general population shows that workers are significantly less likely to have most diseases than the overall population. This is believed to be related to the fact that in order to hold a regular job for a prolonged means that one cannot have a debilitating disease, as one might see in non-workers included in the general population.

This study found, in general, that workers had less cancer and other diseases than the general population. There were some findings that suggested that some cancers previously associated with radiation exposure were somewhat elevated in this population as well. There was also some suggestion of a relationship between exposure to trichloroethylene, a commonly used chemical, and a cancer called non-Hodgkin's lymphoma, and between metals exposure, specifically arsenic, and risk of suicide.

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The study completes a mortality analysis of the last uranium enrichment facility in the United States that had not previously been studied in detail. It provides further support for previously published observations of the relationship between radiation exposure and hematopoietic cancers, and provides intriguing suggestions of a relationship between trichloroethylene exposure and non-Hodgkin's lymphoma, and between metals exposure, specifically arsenic, and risk of suicide.

Completion of the study also provides an opportunity to now consider a combined analysis of the three uranium enrichment facilities: Oak Ridge, Portsmouth, and Paducah.

SECTION 2 ® SCIENTIFIC REPORT

SPECIFIC AIMS

The Paducah Gaseous Diffusion Plant (PGDP) is located in Western Kentucky, about 10 miles west of the City of Paducah. It currently employs approximately 1700 workers; some 8,000 individuals have worked at the plant since it was opened in 1952. The plant is located in a rural area, adjacent to protected conservation, wildlife and recreation areas. The primary function of the PGDP has been to produce enriched uranium for use by commercial reactors or as feed material for other plants that further enrich the uranium. Workers, government officials and the surrounding community have raised concerns about potential health effects from current and past exposures at the plant. The studies proposed here completed a previous mortality investigation to help address those concerns. Following recommendations received from NIOSH, the study was constructed in three phases: (1) a feasibility study that was completed in January, 2003; (2) a pilot study scheduled completed in July, 2004; and (3) funding for the final phase of the study was completed on June 30, 2009. Completion of the mortality study entailed combining work histories with historical exposure data to create an exposure metric for each worker at the plant, throughout the history of the facility. The following steps were taken to achieve that goal.

In Specific Aim 1, we validated the worker roster against other existing name lists (Oak Ridge Operations, USEC, PACE) and source documents (e.g., beneficiary claims, exposure reports, and personnel records). These rosters compiled by differing sources should provide an intercept of true' PGDP workers..

In Specific Aim 2, we developed a comprehensive list oflobs and job histories for the workforce from paper records, electronic files and employee interviews.

In Specific Aim 3, we created a Job Exposure Matrix for chemical and radiation exposures throughout the history of the plant. The job exposure matrix (JEM) was primarily used to assess chemical and internal radiation exposures and for external radiation exposures for the few employees who were not badged. For workers wearing radiation badges, the actual exposures recorded in the badge data was used for exposure reconstruction.

In Specific Aim 4, we linked the Work History data with the Job Exposure Matrix to estimate individual worker exposures. By merging the work history and the qualitative JEM, a group of exposure metrics were constructed. For persons employed in one or more operations associated with potential exposure, the total number of years of exposure was calculated.

In Specific Aim 5, we evaluated worker Mortality for relationships with workplace exposures using standardized mortality ratios and risk assessment approaches. The data analysis included an all-cause life table analysis and a longitudinal modeling approach for specific cancers of interest. The life table analysis produced summary estimates of relative risks over the entire cohort experience using external referents, providing an overview of mortality patterns in the PGDP cohort but is not specific for any individual exposures. The second phase of the analysis was to estimate relative risks of selected cancers as a function of external and internal radiation, as well as various chemical exposures, adjusted for potential confounders such as age, race, and gender.

Finally, in Specific Aim 6, we will communicate the study results to employees and management. This phase of the project is in its planning phase, awaiting completion of the above analyses. The benefit of these investigations can only be fully realized by translation of interpretable findings into concepts that can be passed on to the workers and management at the Paducah facility. Direct communication with these two groups will help provide a balanced perspective on the inherent and perceived risks as well as benefits of working at the plant and the latest medical information on preventive measures against diseases influenced by radiation exposures.

The overarching goal of these investigations is to evaluate the impact of historical exposures on worker mortality. The PGDP was the only remaining gaseous diffusion plant in the US that had not undergone a comprehensive occupational health study. The data generated by the PGDP investigations will be available to merge with the two prior studies at the Portsmouth and Oak Ridge gaseous diffusion plant facilities. The Paducah data will add substantially to the statistical power of the combined database to address the pressing health concerns of uranium enrichment workers.

BACKGROUND AND SIGNIFICANCE

History of the Paducah Gaseous Diffusion Plant (PGDP)

The PGDP is located in McCracken County, Kentucky, approximately ten miles west of the City of Paducah and three miles south of the Ohio River. The site occupies about 3,425 acres, 750 of which are within a security fence, and contains uranium enrichment process equipment and support facilities. Commissioned in 1952, the current mission of the Plant is to "enrich" uranium for use in domestic and foreign commercial power reactors. Enrichment involves increasing the percentage of uranium-235 in the material used for creating reactor fuel (UF6). Uranium-235 is highly fissionable, unlike the more common isotope uranium-238. The PGDP enriches the UF6 from roughly 0.7 percent uranium-235 to about 2.75 percent uranium-235. The Department of Energy (DOE) is the site "landlord," owns the physical plant, and is responsible for overall operation of treatment systems for underground contamination (plumes), including the Northwest plume and the Northeast plume pump and treatment systems and for operation of the facility and environmental management, compliance and restoration. The plant production operations are managed by an independent company, the United States Energy Corporation (USEC). Bechtel Jacobs Corporation (BJC) is the management and integrating contractor for DOE site remediation activities since April 1998. BJC relies on subcontractors to conduct environmental restoration and waste management functions. Thus, exposure and personnel records are held by DOE, USEC, or BJC, depending on the time frame when the data were collected and the employment status of the worker. Most of the important historical data are held by USEC.

As a consequence of the production of enhanced uranium at the Paducah facility, there have been numerous instances of release of various forms of contamination in the surrounding plant vicinity. While the PGDP has carried out extensive monitoring of external radiation exposure, data on internal radiation exposures encountered at the plant are limited. The internal dosimetry program at the

Paducah plant has in the past primarily focused on routine uranium urinalysis and for the most part, internal exposure to uranium was considered to be a chemical rather than radiological hazard (Baker, R.C. and Russell, A.W., 1965; Baker, R.C. and Davis, K.A., 1967; Davis, K.A. and Brown, E.G., 1969). A 1960 memorandum raised issues relating to neptunium exposures and stated that there were "possibly 300 people at Paducah who should be checked out (for neptunium exposures)" (Paducah Report 1970; Paducah Report 1974). Based on ICRP methodologies and several sets of generally conservative assumptions, some internal dose estimates for neptunium-237, plutonium-239, thorium-230 and uranium were made for selected jobs. The dose estimates were made based on available historical gross alpha air sampling data along with estimates of the radionuclide percentages characteristic of certain operations. Internal dose estimates were only calculated for operations identified as having an increased potential for transuranic exposures and for which area air sampling data were available. Surveys, performed as recently as 1991, indicate transuranic materials in many of the process buildings at the site. This raises the possibility that other groups of workers may have been exposed to these materials. It was determined that some workers could have had internal radiation exposures that may have exceeded regulatory limits. Finally, a recently released report of a study undertaken by the Paper, Allied Industrial, Chemical and Energy Workers and the University of Utah provides important information about the levels and types of radiation exposures probably encountered at PGDP (PACE 2000).

Previous Mortality Studies of DOE Workers

The proposed cohort mortality study will attempt to investigate the risk of developing a fatal disease, especially cancer, associated with radiation and chemical exposure at the PGDP. Previous studies of workers at DOE facilities have been somewhat equivocal. A study of all Oak Ridge facilities (TEC, Y12, X-10, and K-25) found higher mortality rates in the K-25 workers compared to the X-10 and Y-12 employees (Frome, et al. 1997). Cancer incidence could not be assessed owing to the absence of a population-based cancer registry in Tennessee. The K-25 facility is similar to PGDP in that it was also a uranium enrichment plant. However, most of the excesses were in non-cancer mortality. Only lung cancer was significantly elevated, and leukemia actually showed a negative dose-response. All radiation analyses were for external radiation from badge data, with no attempt to examine internal radiation. Cragle, et *al.* (1996) found a statistically significant dose-response relationship for lung cancer and external radiation at the Fernald facility outside Cincinnati, Ohio. With only limited data available on internal exposure, no significant dose-response was found. Dupree, et *al.* (1995) reported results of a case-control study of lung cancer for workers at Fernald, TEC, Y-12, and Mallinckrodt facilities. They found no significant relationship with internally deposited radionuclides. They reported an odds ratio of 2.0 for workers exposed to 25cGy (25 rem) and higher, but this estimate was highly uncertain. Several other studies of different DOE sites found no elevation in lung cancer rates (Gilbert, et a1.1993; Acquavella, et al. 1985; Wilkinson, et al. 1987). A mortality study of a uranium enrichment plant was conducted by Frome and others (Frome et al. 1990) involving the K25 plant in Oak Ridge TN. This study examined mortality patterns among workers who were employed at least one month during World War II in the Oak Ridge facilities of X-10, K-25, and Tennessee Eastman Corporation (now Y-12). This study examined both SMRs and exposure response trends using Poisson regression models. Vital status was ascertained through 1980 for 28,000 white male workers. The SMR for all causes was 1.11 using U.S. rates as referents, with an increasing trend of 0.74% per year. The excess mortality was primarily due to lung cancer and diseases of the respiratory system. Lung cancer rates in the K-25 facility were approximately 16% higher than the U.S. rates with a significantly increasing trend over the period from 1950 to 1980. The SMR for leukemia was also elevated, but was not statistically significant.

The most recently published study of a new population of nuclear workers examines the mortality experience of employees at the Rocketdyne/Atomics International plant in California (Ritz, et al. 1999). This study found a significant dose-response with external radiation for all cancers, hematopoietic, and lung cancer for workers exposed above 200m 5v (20 rem). Except for leukemia, all cancers showed a mortality rate less than expected compared to U.S. rates, a fact which emphasized the strong healthy worker effect (HWE) in nuclear worker cohorts. No trends were found for cancer mortality to be associated with internal radiation exposure or chemical exposures. In addition to the Rocketdyne study, three other nuclear workers cohorts found significant associations between external radiation dose and leukemia. Wing and colleagues (1991) found a significantly elevated SMR=1.63 for leukemia in workers at Oak Ridge National Laboratory. They also found a significant dose-response relationship for all cancers, but not for any individual cancer, including leukemia. Douglas, et at., (1994) found a significant dose-response for leukemia and external radiation doses received by workers at the Sellafield plant of British Nuclear Fuels. For cancers other than leukemia, dose-response estimates were not significant and in fact were well below those reported for atomic bomb survivors. A Canadian study published by Gribbin, et al. in 1993 found a borderline significant (P=.058) dose-response for leukemia and external radiation received by workers at Atomic Energy of Canada. This, however, was based on only 4 cases and therefore should be interpreted with caution. They also found a positive, but not statistically significant, association with all cancers.

In addition to these studies of individual facilities, a study of combined nuclear worker cohorts found a significant association between radiation and leukemia. Cardis, et a1. (1995) studied a population of over 95,000 nuclear workers from the U.S., the U.K. and Canada who were monitored for external radiation. Cumulative external radiation exposure was found to be significantly related to leukemia, excluding CLL. They also found a significant dose-response relationship for multiple myeloma, but not for any other individual cancer or for all cancers combined.

The examination of cancers other than lung cancer and leukemia among nuclear workers has been negative with only a few exceptions. Ten studies have been published between 1979 and 1991 regarding the association of brain cancer and occupational radiation exposure in nuclear workers. Only one showed a significantly elevated risk for brain cancer. This was a study of workers at a thorium production facility and was based on only 3 brain cancer deaths among 592 workers (Polednak *et al.* 1983). A recent meta-analysis of these 10 studies estimates a borderline significant standardized mortality ratio (SMR) for brain cancer of 110 (CI 99-122). An early unpublished NIOSH report on the Portsmouth Gaseous Diffusion Plant found an increase in stomach cancer, but the excess was not statistically significant (Brown and Bloom, 1987).

A study that has particular relevance for the proposed PGDP investigation was a report on the Portsmouth Gaseous Diffusion Plant in Piketon, OH, released in October, 2001 (NIOSH 2001). This plant has roughly the same size and mission of the Paducah plant, although the Piketon plant enriched uranium to a much higher weapons-grade level. The Piketon study estimated worker exposures to external and internal radiation; chemical compounds of uranium, nickel, and fluorine; and electro-magnetic fields (EMF). The external radiation data for personal exposures were the most prevalent and of the highest quality, with over 81% of the cohort having badge data. Approximately 47% of the workers had at least one urine analysis record for internal radiation exposure. No internal dosimetry modeling was done for individual workers. Instead, urine analysis alpha counts were used as a surrogate for internal dosimetry. Since data were not available for all workers or time periods, a job-exposure matrix (JEM) approach adjusted for frequency of monitoring was used to assign alpha levels to all workers. Although a wide variety of chemical exposures were present at the Piketon site, a sufficient quantity of data were only available to estimate exposures to uranium metal, nickel, fluorine, and fluoride compounds. Most records came from area samples, which required a broadly defined JEM approach to be employed. Since no historical measurements were available for estimating EMF exposure, surveys were conducted between 1993 and 1995 to measure 60 Hz fields. These data were used to define 26 individual exposure groups based primarily on the worker's location in the plant. Exposure to EMF was assumed to be constant over time, since the primary sources of EMF (large electric motors) changed very little from the initial years of plant operation. Cause-specific mortality was examined for 92 causes of death using standardized mortality ratios (SMRs) with U.S. mortality rates as referents. In addition, nested case-control studies were conducted for lung cancer, hematopoietic cancer, leukemia, and stomach cancer. Results of the SMR study for mortality through December 31, 1991 showed an all-cause SMR = 0.72 based on 1,088 deaths (12%). The all cancer relative risk (SMR = 0.82) was also less than expected using U.S. rates as the comparison. There were no statistically significant elevated SMRs for any individual cancer. However, non-significant elevations were reported for stomach cancer (SMR = 1.18), female genital organs (SMR = 1.27), bone cancer (SMR = 1.68), lympho-reticulosarcoma (SMR = 1.37), and Hodgkin's disease (SMR =1.38). No particular temporal pattern in mortality rates was noted.

The four case-control studies were generally negative. Exposure-response analyses were performed in each study for both external and internal radiation exposure. Because of the lack of quantitative data on chemical, metal, and EMF exposures, these exposures were categorized as ever or never exposed to each agent. Exposures were lagged from 0 to 20 years in five-year increments. No statistically significant exposure response relationships were found for any of the cancers or exposure agents in the overall analyses. The lone exception to the negative findings was a statistically significant effect modification by age for leukemia associated with both external and internal radiation exposure. This effect indicated that there was a significant exposure-response associated with both internal and external radiation exposure among younger workers. No positive effect was indicated for workers over 40 years of age.

In summary, previous analyses of mortality among gaseous diffusion plant workers have yielded mixed results. The PGDP is the only remaining gaseous diffusion plant in the US that has not undergone a comprehensive occupational health study. While many exposures at PGDP were likely to be similar to those experienced at other plants, there were also other non-diffusion plant activities carried out at the Paducah facility under the "Work for Others" program that included radiation and chemical exposures. The data generated by the PGDP investigations will be available to merge with the two prior studies at the Portsmouth and Oak Ridge facilities, adding substantially to the statistical power of the combined database to address the pressing health concerns of uranium enrichment workers.

Literature Review and Chemicals List

Preliminary Industrial Hygiene data from PGDP have demonstrated (not surprisingly) that a wide variety of chemicals and metals were present in the plant environment. Based on this information and discussions with former workers, we have identified seven agents that were likely present in high levels at the plant: arsenic, asbestos, beryllium, cadmium, chromium, trichloroethylene, and PCBs. We anticipate that there may be many additional chemicals, including many carcinogens, identified as we complete our data collection, and we will incorporate this information into the study. A complete review of their toxicology is beyond the scope of this proposal, but the following is a brief summary of human health effects with a particular focus on cancer. For additional detail, the reader is referred to the ATSDR Tox Profiles 2003 (ATSDR 2003). Compounds are reviewed in alphabetical order.

Arsenic: A large number of epidemiological studies have shown that inhalation exposure to inorganic arsenic increases the risk of lung cancer. Enterline and Marsh (1982) studied arsenic-exposed workers at the ASARCO copper smelter in Tacoma, Washington and found a significant increase in respiratory cancer mortality (SMR=189.4) based on 104 observed respiratory cancer deaths in a cohort of 2,802 male workers employed between 1940 and 1964. In a follow-up analysis of the same cohort with improved exposure estimates, lung cancer mortality was shown to follow a concentration-response pattern (Enterline 1987a), a finding confirmed by Mazumdar (1989) and extended in a later report with longer follow-up (Enterline 1995). Lee-Feldstein (1986) found a significant increase in respiratory cancer mortality (SMR=285) based on 302 observed respiratory deaths in a cohort of 8,045 white male workers employed between 1938 and 1956 at the Anaconda copper smelter in Montana. Welch et al. (1982) analyzed a subset of this cohort (n=1,800), that included information on smoking and other occupational exposures, and was able to demonstrate a consistent dose-response relationship with arsenic exposure. Enterline et al. (1987b) carried out a larger cohort study of 8 US copper smelters with similar findings, and studies at the Ronnskar copper smelter in Sweden provided further confirmation (Jarup 1991; Jarup 1989). Other cancer types have been reported to be potentially associated with inhalation exposure to inorganic arsenic, but strong evidence is lacking.

Asbestos: There is an extensive literature documenting the relationship between asbestos exposure and lung cancer and mesothelioma; only a few key reports will be highlighted here. Selikoff et al. (1979) in a classical study of 17,800 insulation workers (men) in the United States and Canada found a 4.6 fold increase in lung cancer over expected rates. An EPA review (1986) reported statistically significant ($p<0.05$) increases in lung cancer mortality in 32 of 41 recent studies. Goodman et al. (1999), in ameta-analysis of 69 asbestos-exposed occupational cohorts, calculated a lung cancer meta-standard mortality ratio (SMR) of 1.63 (95% confidence interval [CI] =1.58-1.69). Lung cancer has also been reported in household members of asbestos workers, attributable to asbestos contamination of work clothes (Magnani 1993). Selikoff (1979) also reported an increase in mesothelioma among asbestos exposed workers, a finding that has been repeated by numerous later studies (for example, McDonald 1980; Spirtas 1994; Teschke 1997). Gastrointestinal cancers have also been reported in association with asbestos exposure by some researchers. (Selikoff et al. (1979) reported 99 deaths from cancers of the esophagus, stomach, colon, or rectum compared to 59.4 expected in their cohort of 17,800 insulation workers, and McDonald et al. (1983) observed 26 deaths from gastrointestinal cancer compared to 17.1 expected in a cohort of 2,500 asbestos textile workers, with adose-response relationship to cumulative exposure to asbestos. Two meta analyses of available cohort studies by Frumkin and Berlin (1988) and Homa et al. (1994) confirmed the relationship between asbestos exposure and gastrointestinal cancer mortality, while other reviewers contend that a causal relationship between occupational exposure to asbestos and the development of gastrointestinal cancers has not been established (Doll and Peto 1985, 1987; Edelman 1988, 1989; Goodman et al. 1999; Weiss 1995).

Beryllium: Mancuso (1980) in a fourth follow-up study of beryllium workers in Ohio and Pennsylvania found an increase in lung cancer deaths among workers chronically exposed to beryllium. A study by NIOSH and OSHA found a significantly increased risk of lung cancer among beryllium workers at one facility in Reading, Pennsylvania (Wagoner 1980). However, a number of investigators have criticized these studies and attributed the increases in lung cancer to confounding by cigarette smoking [EPA (1987), MacMahon (1994), and Bayliss (1980)]. More recently, Ward et al. (1992) studied a cohort of 9,225 workers employed at seven beryllium processing facilities in Ohio and Pennsylvania, and found an increased risk of lung cancer among exposed workers that increased with longer latency, with a statistically significant SMR of approximately 1.5 after a 30 year latency. In a follow-up study of this cohort designed to acquire more detailed exposure estimation, Sanderson et al. (2001a) observed an overall lung cancer mortality rate of 1.22 (95% C1=1.03-1.43) with higher risk after longer latency periods. Two epidemiological studies of Beryllium Case Registry enrollees (Infante 1980, Steenland 1992) again demonstrated a significant increase in lung cancer risk with an SMR of approximately 2.0. In summary, while many of the studies have limitations, it appears that chronic high level exposure to beryllium is associated with increased risk of respiratory cancer.

Cadmium: The kidney is the primary target organ for cadmium toxicity following long-term exposures, resulting in proteinuria and increased rate of kidney stones. While these conditions, even if they led to chronic renal failure, would not be expected to lead to observable occupation-related deaths, significantly elevated rates of end-stage renal disease have been reported in some occupational cohorts (Elinder et al. 1985; Kazantzis et al. 1988). Although early reports suggested an excess in cancers among cadmium exposed workers, larger more recent studies have not confirmed these findings [for example: Kazantzis (1992) Sorahan (1995) Lamm (1992, 1994); and Sorahan (1997).

Chromium: A number of studies have shown that occupational exposure to chromium (VI) in the chromate production industry is associated with increased risk of respiratory cancer. In an early study, Mancuso and Hueper (1951) observed that 18.2% of deaths among workers at a chromate production plant in Ohio were due to respiratory cancer compared with 1.2% lung cancer deaths among residents of the county in which the plant was located. Rosenman and Stanbury (1996) studied a cohort of 3,408 chromium production workers from northern New Jersey and found an overall risk of lung cancer (proportionate cancer mortality ratio) of 1.51 for white males and 1.34 for black males, increasing with duration of employment and latency. Two studies by Bistrup et al. (1951; 1956) found an elevated risk of lung cancer in chromate production workers in the United Kingdom. In a later follow-up study, 1988 Davies et al. (1991) confirmed that the risk was primarily limited to early years of production at the facilities. Similar results were observed in studies of production facilities in Germany and Japan (Korallus 1982; Ohsaki 1978). Studies of chromate pigment production workers have also consistently shown an association with increased risk of lung cancer, in the U.S. (Sheffet 1982; Hayes 1989), the U.K. (Davies 1979, 1984), Norway (Langrd and Norseth 1975), Germany (Frentzel-Beyme 1983), and France (Haguenoer et al. 1981). Finally, studies of chrome plating workers, while less consistent, also generally support the carcinogenicity of Chromium (VI) (Silverstein 1981; Dalager 1980; Sorahan 1987).

Polychlorinated Biphenols (PCBs); PCBs are clearly toxic to humans. However, there is considerable controversy whether illnesses related to occupational exposure to PCBs would result in mortality that could be detected in occupational health investigations. For example, hepatic effects are well-recognized, but unlikely to be fatal. Attempting to address the limited power of individual studies, Nicholson and Landrigan (1994) combined the results from numerous studies of 3 cohorts and observed a statistically significant increase in cancers of the liver/biliary tract/gall bladder (SMR=285, p=0.008) and biliary tract/gall bladder separately ($p<0.05$, SMR not reported). Kimbrough et al. (1999a) studied capacitor workers and found equivocal evidence of increased mortality from cancer of the intestines (large and small). Three studies suggest a link of dermal PCB exposure to risk of melanoma (Bahn 1976; Sinks 1992; Loomis 1997), but the strength of the association is unclear. The strongest indication of carcinogenicity for PCBs appears to be hepatic and biliary cancers.

Trichloroethylene (TCE): TOE is known to have hepatic and CNS effects, but neither are likely relevant to occupational mortality studies. Epidemiological studies investigating TOE and occupational cancer have been largely negative, but many were limited by size or cohort, length of follow-up and multiple chemical exposures (Axelson 1986; Axelson 1978, 1994; Malek 1979; Shindell 1985; Spirtas 1991). Several studies have reported positive associations with various cancers, but none could reliably relate the outcomes to exposure to TOE since other chemicals with known toxicities were present (Antilla 1995; Henschler 1995; Hardell 1994; Blair et al. 1979). Thus, the evidence for carcinogenicity of TOE in humans is limited.

METHODS

Aim 1. Validate the worker roster against other existing name lists and source documents.

The cohort was assimilated from several overlapping sources, then, de-duplicated to generate a complete cohort of unique workers. Cohort enumeration consisted of identifying eligible worker population from employee personnel records from the DOE and its contractors USEC, and BJC, and then verification of eligible workers from Oak Ridge Associated Universities (ORAU) records and PACE union membership listings. A major problem encountered when linking the data sets and eliminating duplicate records was the identification of inconsistent or incorrect data in 1 or more employee records. Often, information from different sources about a given employee was inconsistent or had incorrect information. This included inconsistent or incorrect social security numbers, dates of birth, and names, especially with regard to women who married after their initial hire date. In these cases, extensive investigations in all data sets were carried out to resolve the discrepancies. Errors were corrected when 2 or more researchers would review the data and link consistent data found between the 5 different data sets.

<u>Personnel Records</u>

Personnel records were found in three locations. These include DOE contractors USEC and BJC, and DOE at Oak Ridge. Records from 1952-1993 were kept by USEC at PGDP. USEC was established as an independent contractor in charge of plant operations in 1993. Records from all prime contractors from 1993-1998 were shipped to Oak Ridge in Tennessee and stored. BJC held employment records for their employees from 1998-2003.

Employee Information Yellow Compensation Cards, form WCP-56, hereafter referred to as "yellow cards" were found to contain the most complete information to include work history for each employee. These yellow cards were stored in the personnel file for each employee and became the "gold standard" by which all other records were defined. Each card contained personal identifying information such as name, social security number, date-of-birth, gender, race (although missing often in the early days of plant operations), hire date, department number, job title and change in work history. These yellow cards were consistent and have remained basically unchanged since the beginning of operations at PGDP.

These records were collected from USEC for the time period 1952-1993, and were stored in an electronic format. After extensive investigation and interviews with BJC, USEC, PACE and ORAU, an additional 213 employee records were identified whose personnel record and yellow card had been stored at Oak Ridge. This confusion arose because USEC became an independent contractor of the DOE in 1993 and in 1998 they were privatized and became an investor-owner operation. All records from other prime contractors from 1993-1998 were shipped to Oak Ridge in Tennessee and stored. These 213 hard copies of yellow cards were collected from storage at Oak Ridge for the time period

1993-1998. We collected an additional 138 records for BJC employees for the time period 1998-2001. BJC personnel records were similar to the yellow card except the work history data was not as complete. These personnel records were stored in an electronic database and contained demographic data, job titles, hire and termination dates.

ORAU and PACE Records

ORAU records and PACE membership records were used to resolve missing information, and for matching and intersecting with the personnel records for verification of PGDP employees. Some missing or incorrect data points were found in all datasets. These included social security numbers, date of birth, gender, and race. Linking the ORAU and PACE records with the personnel records validated the completeness of the personnel record.

Aim 2. Develop a comprehensive list of jobs and job histories for the workforce from paper records and electronic files.

The cohort was evaluated for potential exposures by job title. Job titles at the plant were condensed into 44 grouped job titles based on similarity of task and exposures. Briefly, an original list of job titles consisting of 2,727 unique entries was obtained and reduced to 44 grouped job titles. Company representatives and long-term employees provided information about job duties and work organization. To ensure maximum power, analyses were limited to grouped job titles that had a minimum of 100 workers and 5% of the person years for the whole cohort. This reduced the number of individual grouped job titles in the analysis from 44 to 11. An initial analysis of job category outcomes based on gender and race revealed that the sample size was very limited for all categories except white males; therefore, all subsequent job category analyses included only white males.

Aim 3. Create a Job Exposure Matrix for chemical and internal radiation exposures throughout the history of the plant.

The grouped job titles were ranked in a qualitative and categorical manner based on the relative degree of exposure to external radiation, internal radiation, and various chemicals. Because many employees worked several jobs during their tenure at the plant, an analysis plan was devised that accounted for each grouped job title by developing a binary variable indicating whether the employee ever or never held a particular grouped job title.

Aim 4. Link Work History data with the Job Exposure Matrix to estimate individual worker exposure metrics.

Internal and External Radiation Analyses

A surrogate measure, in pg-yrs, of total cumulative internal radiation exposure was derived from urine data to represent cumulative dose of internally-deposited radionuclides. Total cumulative external radiation exposure was taken from badge data and expressed in mrems. A statistical modeling approach used radiation dose/exposure as a continuous variable. For the LTAS analysis, the distributions of internal dose and external exposure were broken into quartiles based on person years at risk. Each quartile was compared to the 1940-2002 U.S. referent population to generate SMRs for all cause, all cancer, and specific mortality outcomes for white males.

Metals and Chemical Exposure Analyses

Relative exposure levels to trichloroethylene and the metals arsenic, beryllium, chromium, nickel, and uranium were developed. This analysis divided the ranks of 0 to 5 into two categories, low or high exposure since individual ranks were often represented by very sparse person-years. Ranks 0, 1, 2, and 3 were assigned to the low exposure category, and ranks 4 and 5 were assigned to the high exposure category. For each exposure, an internal comparison was conducted resulting in an SRR for high exposure to the metal. Due to limited sample sizes for other demographic categories, analyses were conducted for white males only. In order to ascertain if metals exposures resulted in a dose response relationship, a second analysis was conducted by dividing the ranks into three categories: 0 and 1 for low exposure, 2 and 3 for medium exposure, and 4 and 5 for high exposure. The categories were compared to the U.S. referent population to generate SMRs. Again, this analysis was conducted solely for white males.

Aim 5. Evaluate worker mortality for relationships with workplace exposures using standardized mortality ratios and risk assessment approaches

l/ital Stati is

Vital status was determined by linking cohort members' personal identifying information from employee records with data from the U.S. Social Security Administration (SSA), the National Death Index (NDI) and individual state departments of health. All known deceased, and any workers with unknown vital status, were submitted to the NDI for cause of death information. Workers of unknown vital status were counted and considered alive with contributed person years of observation up to the date of termination of employment. For known deaths occurring before 1979, prior to the establishment of NDI, death certificates were requested from departments of health in the state each individual worker was believed to have resided at the time of death.

Cause of Death

A total of 1674 deaths were identified out of 6820 workers in the cohort (24.6%). Deaths were classified and coded to the international classification of diseases (ICD) code that was in effect at the time of death (5t" through 10th revision) for the time period 1952-2003 for 92 causes of death including over 40 cancers. A qualified nosologist coded deaths to the ICD-code in effect at the time of death for all deaths that occurred prior to 1979 and for whom death certificates were obtained. Cause of death was obtained on 1638 out of 1674 deaths (98%) for the entire cohort. Known deaths for which a death certificate could not be retrieved were counted in the unknown cause of death category.

Statistical Analysis

The overall mortality patterns of the PGDP cohort were examined by using LTAS to compare occupational cohort mortality to the U.S. population from 1940 to the present for 92 causes of death including over 40 cancers (National Institutes for Occupational Safety and Health, 2008). Data analysis focused on Standardized Mortality Ratios (SMRs) for the entire period of the cohort (1952-2003), producing summary estimates of relative risks over the entire cohort experience. Expected deaths were calculated by multiplying the person-years at risk (PYAR) in the cohort by the rates in the U.S. referent population. LTAS analysis was used to compare the "cause specific" observed number of deaths with the expected number of deaths (SMRs) in each of the 92 causes of death supplied by LTAS, stratified by race, gender, 5-year age category, 5-year calendar period, job title, metals exposure, and cumulative internal and external radiation exposure.

Statistical significance testing was performed by comparing observed with expected numbers of deaths. P-values were calculated under the assumption that the observed deaths were Poisson variates (random variables with a Poisson distribution) and the expected deaths were estimated without error. Confidence intervals (95%) and two-sided p-values were calculated when the number of observed deaths was less than or equal to ten. For greater numbers of observed deaths, LTAS uses an approximation suggested by Breslow and Day (NIOSH, 2008).

Standardized rate ratios (SRRs) were calculated to compare individual grouped job titles to the rest of the cohort, as well as comparing high to low metal exposures. This internal comparison controls for external factors that may affect outcomes, in particular, the healthy worker effect and regional influences (such as local smoking rates or dietary differences). LTAS uses direct standardization to compare specific outcomes from the job title or exposure of interest to the rest of the cohort (NIOSH 2008).

Aim 6: Communicate the study results to employees and management.

Completion of the research proposed in Aims 1-5 has generated information that will be important to translate into concepts that can be passed onto the management and workers at the Paducah plant. Direct communication with these two groups will help provide a balanced perspective on the inherent and perceived risks as well as benefits of working at the plant and the latest medical information on preventive measures against diseases influenced by radiation exposures. This aspect of the study is currently in the planning stages in collaboration with NIOSH, pending completion of the various ongoing analyses.

RESULTS

Overall Findings

The majority of the cohort was composed of white males (74%). Among the 6820 workers employed at PGDP between 1952 and 2003, 24.6% (1674) were deceased. The vital status of 1% (61) of the cohort remained unknown, and 2.2% (36) of deaths had an unknown underlying cause of death. The largest group of workers was employed at the plant for a period of one to five years (35.5%).

The "all-cause" mortality and "all-cancer" mortality experience of the PGDP cohort was significantly lower than that of the U.S. referent population. The all-cause SMR (SMR=0.73; CI=0.69-0.76) was based on 1638 observed deaths versus 2253 expected (Table 4). The all-cancer SMR (SMR=0.78; C1=0.71-0.85) was based on 461 observed cases versus 592 expected. Deaths related to "Other Causes," which include all deaths that do not have a known cause of death, were also significantly reduced (SMR=0.42; CI=0.27-0.61).

The a-priori cancers of interest (hematopoietic, lung, bone, kidney, and stomach cancers) did not show any statistically significant increased mortality rates. However, individual non-significant excess mortality rates (SMR>1) were noted for cancers of the lymphatic and hematopoietic tissue (SMR=1 .1 9; CI=0.85-1.61). These included non-Hodgkin's lymphoma (SMR=1 .43; CI=0.98-2.01), leukemia (SMR=1.11; CI=0.71-1.65) and multiple myeloma (SMR =1.02; CI=0.49-1.87). Pancreatic cancer was non-significantly elevated although it was not an a-priori cancer of interest (SMR =1.10; 0.75-1.56). Lung cancer had significantly lower mortality rates (SMR=0.72; C1=0.58-0.89).

Outcomes from the analyses of race, gender, 5-year age category, and 5-year calendar period were similar to the overall cohort experience. Ali-cause SMRs were significantly lower than the U.S. referent for all race and gender categories. The 5-year age categories all-cause SMRs were significantly lower than the U.S. referent up to the 70-74 age category. Age categories from 75-89 and above had all-cause mortality rates approximately equal to the U.S. referent.

Individual All-Cause Non-Cancer Mortality

Most mortality rates for non-cancer causes of death were lower in the cohort than the general U.S. population. For example, the SMR for heart disease was 0.75 (C1=0.67-0.83). Non-significantly elevated SMRs were noted for "other nervous system diseases" (SMR=1.30; CI=0.96-1.72), and "other mental disorders" (SM R=1 . 1 1 ; CI=0.62-1.83). Statistically significant excesses in mortality from suicide deaths were observed when stratified by year and age. An SMR of 2.21 (C1=1.01-4.19) for years 1970-1974 and an SMR of 8.13 (C1=1.69-23.75) for years 1975-1979 in the 40-44 age group was found. Further analysis of suicide deaths in the cohort is explored in a separate analysis.

Analysis by Job Title

For most grouped job titles, significantly lower rates of death were found for most cancers and for heart disease. A significant elevation was found for colon cancer for the category Office (SMR=2.73; C1=1.18-7.91). Non-Hodgkin's lymphoma exhibited a significant elevation for the category Security (SMR=3.39; 01=1.10-7.91) and non-significant elevations for Cascade, Chemical Operator, Maintenance, Maintenance/Converter, Maintenance/Custodial, Maintenance/Roads &Grounds and Office. Non-significant elevations for kidney cancer were found for Chemical Operator (SMR of 1.61 [C1=0.69-3.17]) and Maintenance (SMR of 2.13 [C1=0.78-4.63]). Chemical Operator also had an elevation in brain cancer (SMR of 1.52 [C1=0.66-3.00]).

Internal Comparison by Grouped Job Title

Job titles with elevated SRRs for all causes include Maintenance/Converter Shop (SRR=1 .35; C1=0.83-2.17) and Maintenance/Roads &Grounds (SRR=1.25; C1=0.96-1.63). All causes mortality was significantly higher for Security compared to the entire cohort (SRR=1.34; C1=1.06-1.71). Significantly elevated SRRs for specific causes of death included colon cancer for the category Office (SRR=4.91; C1=2.08-11.63), diseases of the heart for Maintenance/Roads &Grounds (SRR=1.70; C1=1.13-2.55) and Security (SRR=1.78; C1=1.17-2.71), lung cancer for Maintenance/Converter Shop (SRR=1.99; C!=1.19-3.35) and Maintenance/Custodial (SRR=2.56; C1=1.09-5.98). Security had a non-significant elevation in Non-Hodgkin's lymphoma (SRR=2.44; C1=0.91-6.55). Examination of the work history of employees who died from Non-Hodgkin's showed that all five held the position before 1955 when Security patrolled all buildings. After 1955, patrols were limited to the periphery.

Analysis of Metal Exposures

For all metals, SMRs for kidney and brain cancers were higher in the high exposure categories compared with the lower exposure categories. However, the internal comparison of metal exposures resulted in no significant elevations in outcomes for those with high exposure. For kidney cancer, these elevations came close to reaching significance for nickel (SRR=3.66; C1=0.99-13.53) and uranium (SRR=3.53; C1=0.95-13.12). There were no significant findings for employees with high exposures compared to those with low metal exposures. Analysis of metal exposures by low, medium, and high exposure also showed no clear dose-response trends.

Internal and External Radiation Analyses

An apparent increase in kidney cancer and multiple myeloma with increasing dose was seen for both internal and external radiation, but was based on few cases. A significant elevation was found for internal radiation exposure for the first quartile for prostate cancer (SMR=2.18; C1=1.09-3.90) and the third quartile for the outcomes Non-Hodgkin's lymphoma (SMR=2.01; C1=1.00-3.60), other nervous system diseases (SMR=1.90; C1=1.11-3.05), and other mental disorders (SMR=2.41; C1=1.04-4.74). A significant elevation for other nervous system diseases was found for the 2nd quartile of external radiation exposure (SMR=1.94; C1=1.03-3.31). No other significant elevations were found for external radiation exposure.

DISCUSSION

This analysis is consistent with the published literature. As expected, a strong healthy worker effect (HWE) was observed in this cohort. PGDP workers experienced lower mortality rates from all deaths

(SMR=0.73) and all cancers (SMR=0.77) compared to the U.S. referent population. The HWE is a common phenomenon that occurs in occupational cohort mortality studies. It results from factors such as selection of the work force, (a working population is generally healthy), changes in lifestyle accompanying employment (employment-associated benefits such as economic gain and medical insurance), and the methodological characteristics of the SMR. Previous studies had suggested that long-term follow-up might reduce this effect. However, another related phenomenon observed more recently in long-term occupational mortality studies is the "healthy worker survivor effect", which tends to diminish exposure related risk estimates in long-term workers because workers who remain employed tend to be healthier than those who terminate.

Despite limitations, SMRs are a critical first step in occupational analyses. It is important to note that results that lack significance do not provide evidence against a true relationship. Despite the overall health of the PDGP cohort, lymphatic and hematopoietic cancers reflected a non-significant elevated SMR of 1.19 based on 68 observed deaths. Non-Hodgkin's lymphoma, leukemia and multiple myeloma SMRs were elevated. Non-Hodgkin's lymphoma showed the most prominent excess (SMR=1 .43; 32 observed deaths).

The internal comparison using SRR's reduces the HWE due to differences between the occupational populations compared to the general U.S. population and therefore may address some of the SMR limitations. In particular, the healthy worker effect and regional influences (such as local smoking rates or dietary differences) are controlled for. The internal comparison showed that the job titles Maintenance/Converter Shop, Maintenance/Roads & Grounds, Office, and Security had higher, but non-significant, Non-Hodgkin's lymphoma deaths compared to the rest of the cohort. These job titles were not known to have regular radiation exposure. However, prior to 1955, Security did patrol all buildings, and may have poorly characterized exposures. Examination of the work history of Security employees who died from Non-Hodgkin's lymphoma showed that all five held the position before 1955. Management and long term employees indicated that Chemical Operators had higher exposures to radiation (Hahn, 2005). In examining the SRRs for lymphatic and hematopoietic cancers, Chemical Operators had higher death rates than the cohort for leukemia and multiple myeloma but not Non-Hodgkin's lymphoma.

These findings support trends for hematopoietic cancer risk found in similar cohorts. Hematopoietic cancers are of major interest because of the recognized association with radiation exposure. It is well documented that high dose radiation exposure has resulted in immunosuppressive and carcinogenic effects in organs where radionuclides concentrate, specifically for most forms of leukemia. Previous DOE studies have also revealed increased SMRs for hematopoietic cancers with low dose radiation exposure, although not always statistically significant. Non-Hodgkin's lymphoma and leukemia showed consistently increased SMRs, an observation supported by this present study.

A significant elevation in colon cancer was found in the grouped job title, Office. This job category also showed non-significant elevations in pancreatic cancer, Non-Hodgkin's lymphoma, and leukemia. Employees with this job title did clerical jobs, but their offices were located in production buildings, and they may have had transitory exposure to some chemicals. Office workers typically perform more sedentary tasks, and may not exhibit the HWE to the same degree as employees who execute more physical tasks.

Select job titles underwent further analysis with the neurodegenerative disease rate file. Elevations in the "other nervous system diseases" outcome were found to be the result of increases in deaths from Alzheimer's disease. As is typical for this disease, deaths from this outcome primarily occurred in individuals over the age of 70, many in their 80s. Reductions in deaths from heart disease and cancers may account for the increase in Alzheimer's deaths.

The metals analysis showed elevations in kidney and brain cancers for all metals, nearly reaching significance for nickel and uranium. The job titles that had high exposures to nickel and uranium included Chemical Operator and Maintenance. Both of these job categories had non-significant elevations for kidney cancer, and Chemical Operator also had an elevation in brain cancer. Several other maintenance job titles had high exposures to these metals, but had limited person years at risk, and therefore were not analyzed separately. A dose-response trend was not evident for any metal exposure. A limitation of the metals analysis was that job titles that had higher exposures for one metal tended to have high exposures to all metals, making it difficult to determine an association between a particular metal and an elevated outcome.

No trends from cumulative internal or external radiation exposure were apparent. Exposure to radiation at the plant followed a log-normal distribution, with the majority of employees accumulating little exposure. The categories for radiation exposure were quartiles based on person years at risk. This strategy resulted in very low exposures in the lower quartiles, which may have masked evidence of a dose-response relationship. A second analysis is employing modeling techniques to further explore radiation exposure-disease relationships.

Limitations to this analysis included lack of smoking data. Based on previous studies similar in scope, it was not anticipated that smoking rates would be significantly different between different groups of exposed and unexposed workers and thus would not adversely impact this analysis.

In conclusion, this study provides continued support for the relationship between radiation exposure and hematopoietic cancers, especially non-Hodgkin's lymphoma, although the low radiation dose levels precluded the detection of statistically significant results. Other cancers and causes of death warranting further investigation are brain cancer, breast cancer, suicide deaths and depression.

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PUBLICATIONS

Journal Articles

Bahr, DE, Hughes T, Aldrich TE, Silver KZ, Brion GM, Tollerud D [2009] "Cohort Follow-up: the 21st Century Procedures," Journal of Registry Management, 36:1:16-20.

ABSTRACT: The basic logic of designing an occupational cohort study has changed little since William R. Gaffey outlined the issues of follow-up, measurement of exposure, and analysis of data. However, many new avenues of tracking workers for epidemiological studies have been developed since Gaffey wrote his paper in 1973. Many disease registries also perform follow-up of subjects for vital status determination, so the procedures used with this process are common to the two applications. This article speaks to cohort construction for this occupational research as well as describes the 2007 methods for vital status follow-up. Rises in concern about work-related disease risks and the scientific resources for performing these studies coincided with the computer revolution. Government and private sources of data on vital status have changed in several ways over the 35 years since Gaffey's seminal paper. Some systems make the process of follow-up more rapid and productive, and some barriers have been imposed as societal concerns for privacy have risen. We describe the process of linking 5 sources of data to compile a roster of 6,820 workers employed at the Paducah Gaseous Diffusion Plant from 1953 to 2003. The record linkage processes achieved a final death cohort of 1,672 deaths—the ascertainment of these deaths (by time period) was 1,379 (1979-2003) and 293 (1953-1978); follow-up then was 100% for this cohort.

Saman DM, Reinhart NL, Aldrich TE, Brion GM. "Regional Diversity for Leukemia Survival in Kentucky (1996-2000)," KY Med Journal [In Press]

ABSTRACT: The analysis reveals greater district-to-district variation in leukemia median survival periods than would be expected by chance alone. More importantly, the Purchase ADD has lower leukemia median survival times than the nation, Kentucky, and most other area development districts in the comparison. Perhaps curiously, the poorest survival in the state is found in urban and industrialized areas, not in the rural, poorer and Appalachia regions. Failure to appreciate this regional variation could bias findings of studies for a regionally resident population.

Chan MC, Hughes TS, Muldoon S, Aldrich T, Rice C, Hornung R, Brion G, Tollerud D, and The Paducah Gaseous Diffusion Plant Project Team. "All Cause Mortality Among Paducah Gaseous Diffusion Plant (PGDP) Workers." [In preparation]

ABSTRACT: This was a retrospective occupational cohort mortality study of 6,820 workers employed at the Paducah Gaseous Diffusion Plant (PGDP) for a minimum of 30 days from 1952-2003. This study was to determine if workers had higher all cause, cancer, or non-cancer mortality rates than the general population as a consequence of employment in the production of enriched uranium, and to ascertain whether employees with certain job titles, or with higher exposures to five metals, internal or external radiation experienced elevated death rates compared to the rest of the cohort.

Methods: Deaths in the cohort were compared to expected death rates in the 1940-2002 U.S. population to produce standard mortality ratios (SMRs) with confidence intervals. Job titles were grouped by similarity of tasks and exposures. Death rates from job titles were compared to both the 1940-2002 U.S. population and to the rest of the PGDP cohort, generating SMRs and standardized rate ratios (5RRs). Both total cumulative internal radiation dose and external radiation exposure were divided into quartiles and analyzed by comparing each quartile to the U.S. referent population. Relative exposure to each of five metals was stratified into low and high exposure groups to generate SRRs.

Results: Overall mortality and cancer rates were lower than the referent U.S. population (all causes SMR= 0.73; CI =0.68-0.77), (all cancers SMR = 0.78; C1=0.69-0.88). Individual non-significant excess mortality rates were noted for cancers of the lymphatic and hematopoietic tissue (5MR=1 .1 9), non-Hodgkin's lymphoma (5MR=1 .43), leukemia (5MR=1.11), multiple myeloma (SMR=1.02) and cancer of the pancreas (SMR= 1.10). For most outcomes, the job title analysis reflected a strong healthy worker effect across job titles. Significant elevations were found for colon cancer for the job category Office (SMR=2.73), Non-Hodgkin's lymphoma for the category Security (SMR=3.39), and other nervous system diseases for the category Chemical Operator (SMR=1 .65). In addition, significant elevations were found for Alzheimer's disease for the job categories Engineer (SMR=4.16) and Maintenance (SMR=3.19). Analysis of metals found elevated SRRs for kidney and brain cancers, with nickel and uranium almost reaching significance for kidney cancer. No evidence of aexposure-response relationship was found. The cumulative internal and external radiation analyses found no major trends.

Conclusion: This study provides additional support for the relationship between radiation exposure and hematopoietic cancers that are consistent with previous studies. Increased rates of Alzheimer's- deaths were found for some job titles, suggesting a strong healthy worker effect.

Figgs L, Holsinger H, Freitas S, Aldrich TE, Brion GM, Tollerud DJ. "Suicide among Arsenic Exposed Workers at the Paducah Gaseous Diffusion Plant in Paducah, KY (1953 — 2003)" [In-Preparation]

ABSTRACT: Prior observation suggested that arsenic exposure was associated with poor mental health outcomes. We asked if suicide mortality risk among Paducah Gaseous Diffusion Plant (PGDP) workers with a high likelihood of arsenic exposure was different than PGDP co-workers with no or low arsenic exposure likelihood. A dynamic, retrospective cohort of nuclear industry workers (N = 6,820) employed from 1953 to 2003 was assessed for arsenic, beryllium, chromium, nickel, and uranium exposures (job exposure matrix) and suicide risk (proportional hazard regression).

Results: Workers committing suicide were typically older, white, males with higher likely exposures to arsenic, beryllium, nickel, and uranium than workers who did not commit suicide. Hazard ratio estimates for suicide risk associated with high exposure likelihood to arsenic compared to workers with no or low arsenic exposure likelihood ranged from 2.5 (1.2 — 5.0, crude) to 12.7 (2.1— 77.2; adjusted).

Conclusion: Suicide risks are not equal among PGDP workers with a high likelihood of exposure to arsenic compared to workers with no or low arsenic exposure likelihood. There is a statistically significant (alpha < 0.05) two to four fold excess of suicides among workers with a high likelihood of arsenic exposure compared to workers with a no or low arsenic exposure likelihood.

Bahr DE, Aldrich TE, Seidu D, Brion GM, Tollerud DJ, and the Paducah Gaseous Diffusion Plant Project Team. "Occupational Exposure to Trichloroethylene in Paducah Gaseous Diffusion Plant Workers" [In-Preparation]

ABSTRACT: The Paducah Gaseous Diffusion Plant (PGDP) is a uranium enrichment plant that became operational in September, 1952. The PGDP is located approximately 10 miles west of the city of Paducah in the western part of Kentucky. This is the only gaseous diffusion plant in the United States that has not undergone a mortality study. Concerns have been raised about the adverse health effects that workers may have suffered while working at the plant, including exposures to chemicals. Trichloroethylene (TCE) is a nonflammable, colorless liquid at room temperature with a sweet odor and a sweet, burning taste. TCE is taken up by direct contact through the skin, ingestion, and by inhalation. Moser established that workers at PGDP were exposed to TCE primarily in departments that clean the process equipment as TCE was used to degrease fabricated metal parts.

The Life Table Analysis System (LTAS) program developed by NIOSH was used to calculate the SMR for the worker cohort and SRR relative to exposure to TCE. LTAS calculated a significantly low overall SMR for these workers of 0.76 (CI 0.72, 0.79). A review of three major cancers of interest to Kentucky produced significantly low SMR for trachea, bronchus, lung cancer (0.75, CI 0.72,0.79) and high SMR for Non-Hodgkin's lymphoma (1.49, CI 1.02,2.10). No significant SMR was observed for leukemia and no significant SRRs were observed. In 1885, William Ogel noted two issues when calculating death in industrial workers – "considerable standard of muscular strength" and vigor to be maintained" - introducing the well known healthy worker effect. Healthier workers will seek employment and because of their good health will continue to be employed. Thirty percent of the workers at the PGDP worked more than 40 years at the plant.

Aldrich TE, Freitas S, Brion GM, Tollerud DJ, and the Paducah Gaseous Diffusion Plant Project Team. "Impact of Adding Cancer Incidence Data to a Cohort Mortality Study" [In-preparation].

ABSTRACT: We studied a cohort of 6,820 workers at the Paducah (KY) Gaseous Diffusion Plant [PGDP] for the period 1953 to 2004. Seven-hundred seventy-three [773] of the cohort deaths occurred in Kentucky, 44% of the entire cohort, 459 deaths were due to cancer, 202 in Kentucky. Analyses from the mortality studies have been published elsewhere. The all-cancer SMR was 0.77 (95% CI =0.6999-0.8423). A strong healthy-worker bias was operating.

This article describes a merger of cancer incidence data, with the mortality data from the cohort, for the period 1995-2004. We examined period-prevalence in an attempt to determine how many cancer cases would be added to the study from those who had not expired. The entire cohort experienced 146 lung cancer deaths, 64 of which were in Kentucky. The Kentucky Cancer Registry located 71 lung cancer cases, seven more

than the mortality study included. The cohort study only identified 34 prostate cancer deaths, 17 of which occurred in KY. However, the KCR found 129 prostate cases among the KY residents of the cohort, during this ten year period –112 more cases of prostate cancer that had not expired. The cob-rectal cancer prevalent cases and those for bladder cancer were nearly exactly the expected number. Non-Hodgkin's lymphoma and melanoma had more prevalent cases, than were expected.

Population-based cancer registries may well serve occupational studies beyond the conventional use of only deaths. As cancer survival patterns vary greatly, considerable selection biases may be mitigated over the conventional occupation cohort mortality study.

Aldrich TE, Seidu D, Bahr D, Freitas S, Brion GM, Tollerud D. and the Paducah Gaseous Diffusion Plant Project Team. "Mortality Patterns in a Period Workforce at a Gaseous Diffusion Plant" [In Preparation].

ABSTRACT: We studied a cohort of 6,820 workers at the Paducah (KY) Gaseous Diffusion Plant [PGDP] for the period 1953 to 2003. This article describes a comparison of a group of 754 workers who were employed exclusively during the period 1975-1979 with the 1554 workers who worked in this period as well as other years. This interval was when the gaseous diffusion cascade facilities were re-fit. These `only' period workers have a variety of salient characteristics that distinguish them from the `long term' workforce of the PGDP. The `only 1975-1979' workers had a larger fraction of minorities, and women. This `only' sub-group was disproportionately employed in unskilled labor positions. The `only' workers were younger than the referent group, and present a 14-year earlier mean age at death. There were low standardized rate ratios [SRR] for the major causes of death: cancer, heart. The all-cause mortality SRR was 1.58 [95% confidence limits 0.97, 2.42]. The `only' group was statistically significantly different from the `ever' workers for suicides SRR= 3.74 [based on 11 total events], and for homicides SRR = 11.71 [four total events]. These elevated disease risks seem not to be due to PGDP employment exposures. Socio-economic forces may be a greater determinant for the suicide-murder pattern. These findings pose guidance for communities with a dominant local employer. The persons experience short-term hiring may warrant public health services to mitigate their risk of these tragic deaths. A case-control study of these deaths is recommended to clarify individual risk behaviors.

Aldrich TE, Freitas S, Brion GM, Tollerud D, and the Paducah Gaseous Diffusion Plant Project Team. "Case-Comparison Study of Suicides in a Cohort Mortality Study of an Uranium Enrichment Facility" [In Preparation]

ABSTRACT: Background: We studied a cohort of 6,820 workers at the Paducah (KY) Gaseous Diffusion Plant [PGDP] for the period 1953 to 2003. Significant excess mortality was observed for suicides (SMR=2.19 p<.05) for years 1970-1979 and for ages 40-44 years (SMR=8.12 p< .05). Non-significant elevations of suicide risk were noted for ages 35-54 in each of the five-year increments for the study period. The group of workers employed solely during the 1975-1979 period produced a SRR= 3.74 for suicide.

Methods: This article describes acase-comparison study of all of the Caucasian male suicides in the PGDP cohort (n = 34). Comparison subjects were matched to cases on the year-of-hire within a five-year period [+ 2 years]. Two comparison groups were obtained from within the cohort at a 4:1 ratio: deceased workers, and living workers. Single effects for specific years of employment, age and year of hiring, duration of employment, and years after leaving employment until death. Forward conditional logistic regression was used to identify multiple risk variable configurations.

Results: Many configurations were statistically elevated, but the combination of working less than three years and being 40 years old or younger were the strongest predictor of suicide death in the ten years after ceasing employment at PGDP. Odds ratios of 4.9, 9.7 and 7.9 were found for these factors.

Interpretation: Caucasians men age 40 and younger, who work less than three years for a large, regionally dominant employer should be monitored for at least a decade for risk of suicide.

Freitas S, Aldrich TE, Brion GM, Tollerud D, and the Paducah Gaseous Diffusion Plant Project Team. "Smoking-Attributable Lung Cancer Mortality in an Occupational Cohort" [In Preparation]

ABSTRACT: In Kentucky, the lung cancer mortality rates rose from the lowest quintile before 1970 to lead the nation by 1995. This article describes the impact of divergent secular trends [national versus state] upon the lung cancer mortality experience of workers at the Paducah (KY) Gaseous Diffusion Plant. During the cohort follow-up, the national pattern for lung cancer mortality is observed rather than the Kentucky trend. Such adjustment for regional behavioral risk factor prevalence is important with epidemiologic research.

Hornung R, Rice C, Brewer D, Ho M, Aldrich T, Brion G, Tollerud D and the Paducah Gaseous Diffusion Plant Project Team. "Cancer risk among workers at the Paducah Gaseous Diffusion Plant" [In preparation]

ABSTRACT: This analysis involves statistical analysis of external and internal

<u>Proceedings</u>

Rice C, Hornung R, Moser A, Brewer D, Ho M, Tollerud DJ. [2007] "When 4/2 Does Not Equal 2: Approaches To Extending A Categorical Exposure Rank to a Quantitative Exposure Range." Compendium publication of Collegium Ramazzini meeting, Capri, Italy. October 2007

Pnctprc

Chan MC, Hughes TS, Muldoon S, Aldrich T, Rice C, Hornung R, Tollerud D, and the Paducah Gaseous Diffusion Plant Project Team. [2009] "The Paducah Gaseous Diffusion Plant Mortality Study: Job Title Analysis." APHA, Philadelphia, PA. November 2009

Chan, MC, Muldoon S, Hughes T, Aldrich T, Tollerud DJ. [2008] "The Paducah Gaseous Diffusion Plant Mortality Study: Grouped Job Title Analysis." Research Louisville, Louisville, KY. October 2008.

Reinhart N, Hughes T, Muldoon S, Aldrich T, Tollerud DJ. [2008] "A Model for Occupational Health Studies of Uranium Enrichment Plants: The Paducah Gaseous Diffusion Plant." KPHA, Louisville, KY, March 2008.

Reinhart N, Hughes T, Muldoon S, Aldrich T, Tollerud DJ. [2007] "A Model for Occupational Health Studies of Uranium Enrichment Plants: The Paducah Gaseous Diffusion Plant." APHA, Washington, DC, November 2007.

Saman DM, Freitas SJ, Aldrich TE, Brion GM [2007] "Breast, Lung, Leukemia and Colon Cancer Survival Analysis for USA, Kentucky and Purchase Area Development District: 1996-2000." APHA 135th Annual Meeting and Expo, Washington DC. November 2007.

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