Theses and Dissertations

Fall 2010

Retrospective mortality and cancer incidence study of former U.S. Atomic Energy Commission workers at the Iowa Army Ammunitions Plant in Burlington, Iowa

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RETROSPECTIVE MORTALITY AND CANCER INCIDENCE STUDY OF FORMER

U.S. ATOMIC ENERGY COMMISSION WORKERS AT THE IOWA ARMY

AMMUNITIONS PLANT IN BURLINGTON, IOWA

by

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ABSTRACT

A retrospective mortality and cancer incidence study of former nuclear weapons assemblers from the Iowa Army Ammunitions Plant was conducted. This study examined whether or not workers at the plant exhibited higher rates of mortality or cancer as a result of their work-related activities. Potential exposures included radiation, beryllium, asbestos, and solvents. Cancer incidence was determined by calculating standardized incidence ratios (SIR) and using the Iowa population as reference. SIRs were calculated on 3,889 workers from 1969-2005. Overall and cause-specific mortality was determined by calculating standardized mortality ratios (SMR) and using the U.S. and Iowa populations as reference. SMRs were calculated on 5,743 workers from 1947-2005. The SIR results showed that overall cancer incidence was lower than the Iowa population. Using the Iowa population as reference, the SMR analyses for men demonstrated excesses for all cancers (SMR 1.09, 95% CI 1.02-1.17), lung cancer (SMR 1.38, 95% CI 1.24-1.54), diseases of the respiratory system (SMR 1.15, 95% CI 1.03-1.46), mesothelioma (SMR 6.20, 95 % 1.28-18.1), asbestosis (SMR 9.28, 95% CI 1.12-33.5) and COPD (SMR 1.27, 95% CI 1.10-1.46). Significantly lower SMRs were observed stomach cancer and ischemic heart disease. For women excesses were observed for all cancers (SMR 1.41, 95% CI 1.17-1.69), lung cancer (SMR 2.47, 95% CI 1.72-3.44), ischemic heart disease (SMR 1.32, 95% CI 1.09-1.58), respiratory diseases (SMR 1.59, 95% CI 1.14-2.16), and COPD (SMR 2.47, 95% CI 1.60-3.65). Using the U.S. population, men experienced lower overall mortality while women had significantly higher overall mortality. In conclusion, the SIR portion of the study showed overall lower cancer incidence for both men and women. This may be due to the Healthy Worker Effect and the limited dates of study. There are no cancer registry data before 1969 thus missing cancers with short induction periods. Workers may have also moved out of the Iowa and had a cancer diagnosis in another state. Compared to Iowa

population, there was an excess of respiratory disease deaths and deaths from lung cancer in both men and women. Considering the significant respiratory exposures workers may have experienced, further study with a nested case-control design is suggested.

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A thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Epidemiology
in the Graduate College of
The University of Iowa

December 2010

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PH.D. THESIS

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To Steve, Zachariah, Samuel and Joshua

ABSTRACT

A retrospective mortality and cancer incidence study of former nuclear weapons assemblers from the Iowa Army Ammunitions Plant was conducted. This study examined whether or not workers at the plant exhibited higher rates of mortality or cancer as a result of their work-related activities. Potential exposures included radiation, beryllium, asbestos, and solvents. Cancer incidence was determined by calculating standardized incidence ratios (SIR) and using the Iowa population as reference. SIRs were calculated on 3,889 workers from 1969-2005. Overall and cause-specific mortality was determined by calculating standardized mortality ratios (SMR) and using the U.S. and Iowa populations as reference. SMRs were calculated on 5,743 workers from 1947-2005. The SIR results showed that overall cancer incidence was lower than the Iowa population. Using the Iowa population as reference, the SMR analyses for men demonstrated excesses for all cancers (SMR 1.09, 95% CI 1.02-1.17), lung cancer (SMR 1.38, 95% CI 1.24-1.54), diseases of the respiratory system (SMR 1.15, 95% CI 1.03-1.46), mesothelioma (SMR 6.20, 95 % 1.28-18.1), asbestosis (SMR 9.28, 95% CI 1.12-33.5) and COPD (SMR 1.27, 95% CI 1.10-1.46). Significantly lower SMRs were observed stomach cancer and ischemic heart disease. For women excesses were observed for all cancers (SMR 1.41, 95% CI 1.17-1.69), lung cancer (SMR 2.47, 95% CI 1.72-3.44), ischemic heart disease (SMR 1.32, 95% CI 1.09-1.58), respiratory diseases (SMR 1.59, 95% CI 1.14-2.16), and COPD (SMR 2.47, 95% CI 1.60-3.65). Using the U.S. population, men experienced lower overall mortality while women had significantly higher overall mortality. In conclusion, the SIR portion of the study showed overall lower cancer incidence for both men and women. This may be due to the Healthy Worker Effect and the limited dates of study. There are no cancer registry data before 1969 thus missing cancers with short induction periods. Workers may have also moved out of the Iowa and had a cancer diagnosis in another state. Compared to Iowa

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AEC	Atomic Energy Commission
ALL	Acute Lymphocytic Leukemia
AML	Acute Myelogenous Leukemia
AO	American Ordnance
ATSDR	Agency for Toxic Substance and Disease Registry
BeLPT	Beryllium Lymphocytic Proliferation Test
Bq	Becquerel
CDC	Centers for Disease Control
Ci	Curie
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myelogenous Leukemia
COPD	Chronic Obstructive Pulmonary Disease
DOD	Department of Defense
DOE	Department of Energy
DU	Depleted Uranium
EEOICP	Department of Labor Energy Employees Occupational Illness Compensation Program
ERR	Estimated Relative Risk
FS	Firing Site
FWP	Former Workers Program
Gy	Gray

HSE	Healthy Survivor Effect
HWE	Healthy Worker Effect
IA	Iowa
IAAAP	Iowa Army Ammunitions Plant
IOP	Iowa Ordnance Plant
LLNL	Lawrence Livermore National Laboratory
LANL	Los Alamos National Laboratory
NIOSH	National Institute of Occupational Safety and Health
NRC	National Research Council
NTS	Nevada Test Site
ORNL	Oak Ridge National Laboratory
PIR	Proportional Incidence Ratio
Po	Polonium
Rad	Radiation Absorbed Dose
RAI	Rocketdyne/Atomic International
RCC	Renal Cell Carcinoma
Rem	Roentgen Equivalent Man
RR	Rate Ratio
RSIR	Relative Standardized Incidence Ratio
RSMR	Relative Standardized Mortality Ratio
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
SRS	Savannah River Site

Sv	Sievert
TNA	TN & Associates, Inc
UK	United Kingdom
US	United States
USCOE	U.S. Army Corps of Engineers

CHAPTER ONE: INTRODUCTION

In 1947, the Iowa Army Ammunitions Plant (IAAAP) was designated as the first plant in the nation to assemble atomic weapons (Mason & Hanger-Silas Mason Co., Inc. 2003). The IAAAP is a 19,000-acre operational load, assembly and pack munitions facility located in Middletown, Iowa, located approximately 10 miles west of Burlington, Iowa. This U.S. Government owned facility, under the U.S. Army Industrial Operations Command, is contractor-operated by American Ordnance LLC. American Ordnance (AO) is a joint venture company founded in 1998 and owned by the Day and Zimmerman Group Inc. and the General Dynamics Ordnance Systems Inc. (Day and Zimmerman, Inc 2004). The plant encompasses over 1,000 buildings, 142 miles of roads, and 103 miles of railroad tracks (Mason & Hanger-Silas Mason Co., Inc. 2003). Conventional missile warheads and a variety of large caliber tank ammunitions, mines, mortars, artillery, demolition charges, and weapons' component parts have been produced at the plant. In addition, it is designated as the Midwest Area Demilitarization Facility for the disposition of old and/or obsolete ammunition (Mason & Hanger - Silas Mason Co., Inc, 2003). Built between 1941 and 1943, this establishment was intended to help meet the national munitions production needs in WWII activities. Operated from the beginning by Day and Zimmerman Inc., under a U.S. Army contract, the plant began production activities in mid 1941 (see Table 1.1 for Timeline of AEC Operations). In 1947, production of atomic weapons started under the Atomic Energy Commission (AEC). The AEC regulated the development of nuclear science and technology in addition to conducting research on health issues related to occupational exposures to radiation at nuclear weapon sites (NRC, 2006). In 1977, the Department of Energy (DOE) was created to organize the energy policy programs of the AEC. The DOE subsequently oversaw the radioactive waste disposal programs, energy-related research, the nuclear weapons program, and research

studies of workers at nuclear weapons facilities previously managed by AEC (NRC, 2006).

Operations at IAAAP

At IAAAP, the area designated for the manufacturing of nuclear weapons and other activities was production Line 1 (workers Division B) and surrounding areas. Line 1 is approximately one mile long and occupies 170-190 acres. Line 1 encompasses 250 buildings and related facilities that were all used in some manner in support of the operations related to the fabrication and installation of the shaped charges surrounding the core of the nuclear weapons. IAAAP then partially disassembled the completed weapons for shipping to off-site storage facilities (TNA, 2002). The Firing Site (FS) area comprises 450-500 acres and was developed for testing explosives and ammunition. Operations at the FS were centered on the South Firing Site (FS-6) and the North Firing Site (FS-12). FS operations were supported by 15 structures including administrative buildings, storage magazines, component assembly facilities, and observation bunkers (ATSDR, 2003).

On Line 1, from 1947 until 1962, the first step of the production process included the casting of baratols (the spherical-shaped, explosive charge that surrounds the nuclear weapon's core) and the machining of the casts to ensure a precise fit (TNA, 2002 and USACOE, 2001). Both baratols and "hydroshot" explosive charges (the small hemispheres of explosives used to test the performance of the explosives) may have contained a thin sheet of depleted uranium (DU) (USACOE, 2001). The machining or grinding of these components may have released small quantities of depleted uranium to the machining room environment or to any resultant waste stream. It is reported that the waste material from this process was taken to the Explosives Disposal Area burn pads for disposal by burning (USACOE, 2001). Beginning in about 1962, the process of casting

the baratols was replaced by a new process which involved pressing explosives in a plastic state into molds (TNA, 2002).

Some of the AEC/DOE Line 1 workers were also exposed to ionizing radiation (enriched uranium, plutonium and tritium) through handling of the nuclear weapon's core. Workers routinely handled the radioactive components directly in their hands with only cotton gloves and without lead aprons (Fuortes, 2006). They had little or no radiation monitoring or shielding early on in production.

Both production hazards and health and safety practices at the facility varied and evolved over time. There may have been an increased risk of chemical and radiation exposure during high production (wartime) eras. Workers were potentially exposed to external and internal radiation, organic nitrogen explosives, metals, chemicals (solvents, gases and toxicants), physical heat, and loud noise (CDC, NIOSH document 2001-133). The nuclear materials processed at IAAAP contained depleted uranium, enriched uranium, plutonium, tritium, and radium (ATSDR, 1999). Radioactive cobalt and cesium was used and is present in the environment (ATSDR, 1999). Finally, weapon components were frequently x-rayed for quality assurance, and a sub-set of workers were potentially exposed to external radiation from x-rays and gamma rays (Fuortes, 2001).

During the weapons assembly process at the plant, testing of components occurred at the firing sites and depleted uranium was released into the environment. Data collected from FS-12 in 1974 indicated that depleted uranium was present in the air and the soil (ATSDR, 1999). Following remediation of the areas within Line 1 and the firing site, another radiation survey detected depleted uranium in floor seams and cracks within the buildings. Uranium fragments were found in the soil throughout FS-12. IAAAP was placed on the U.S. Environmental Protection Agency (EPA) National Priorities List in 1990, primarily due to contamination detected in groundwater and surface water. The environmental contaminants of primary interest were based on selected assays revealing

elevated residues along with historically assumed risks of: RDX (1,3,5 trinitro-1,3,5 triazine), DNT (dinitrotoluene), TNT (trinitrotoluene), and lead (US EPA, 2010).

There were several accidents at IAAAP that were isolated to the U.S. DOD production processes. During the WWII era, there were 32 deaths at the plant from explosions in a 2-year period. Records also suggest workers suffered from acute TNT poisoning on several occasions. During one 5-month period in 1943, there was documentation of 1 TNT poisoning fatality and 4 cases of nonfatal systemic TNT poisoning with 39 lost work days (IOP, 1943). From 1966 through 1968, there were 13 fatalities from 5 explosions. Historical records suggest that in response to these incidents there was a dramatic increased focus on health and safety practices with improved training and materials handling (Mason and Hanger– Silas Mason Co, Inc., 1969).

For nearly three decades, conventional and nuclear weapons were manufactured at the plant under separate U.S. DOD and AEC contracts. The production pace peaked during the Korean and Vietnam conflicts when the demand for several types of munitions and warheads grew substantially (Lemert, 1979). It is estimated that the workforce, servicing conventional weapons' lines, varied in numbers from 15,000 around WWII, 7,500 during the Korean conflict, to 5,500 during the Vietnam conflict. In 1975, the production of nuclear weapons was terminated in Iowa and transferred to the Pantex Plant located in Amarillo, Texas (Lemert, 1979). The Pantex studies are pertinent to IAAAP because the cohort is about the same size and the production processes were similar.

The Pantex Plant had three major operations: (1) production of new nuclear weapons; (2) maintenance, modification, and quality assurance testing of nuclear weapons already in the military stockpile; and (3) retirement by disassembly of nuclear weapons no longer required in the military stockpile (Acquavella et al., 1985). The most recent mortality study of workers at the Pantex Plant was completed in 2005 and noted an increase in several cancers including leukemia (Silver et al., 2005). The authors wrote

that the "findings suggest that a future, more comprehensive study might be informative". At the end of Pantex follow-up, only 29% of the early-term subcohort and only 12% of the late-term subcohort were deceased. Retrospective mortality studies or cancer incidence studies have not yet been performed at the IAAAP . As compared to the low percentages of deceased workers at the Pantex Plant, 65% of the former AEC/DOE workers at the IAAAP are deceased. A retrospective cohort mortality and cancer incidence study of workers at IAAAP may provide insights into the health-related impact of work-related exposures at the IAAAP AEC facility and contribute data that could eventually be included in the future pooling of AEC\DOE workers (NRC Report, 1990 and Cardis et al., 2007).

Studies of AEC\DOE nuclear workers contribute to the basic understanding of health risks associated with low-dose radiation exposure in other occupations as well (e.g. the nuclear power industry, airline industry and the medical/dental fields). As the members of the AEC/DOE cohorts age, additional cost effective analyses examining the association between low dose radiation exposure, as well as mixture of chemicals, and adverse health effects is possible since much of the work to establish the cohort is complete. Several former atomic weapons manufacturing sites, including the IAAAP have also had somewhat unique chemical exposures, including beryllium, which may provide important mixed exposure-effect information.

There are a limited number of cohorts today with exposures in the elevated ranges seen in the former munition worker studies, particularly in the early period of plant operation. In fact, these are vanishing cohorts that cannot be replaced if the data are not captured. The IAAAP cohort is smaller than many of the AEC/DOE sites previously studied, but relevant due to unique work environments. Typically, the cost of a retrospective mortality study can be prohibitive under normal circumstances, but this proposed research was performed in conjunction with the congressionally mandated study of non nuclear (DOD) workers thus allowing for an extremely cost-effective study.

Since 2000 the University of Iowa College of Public Health has been participating in the national DOE Former Worker Medical Screening Program (FWP). This program offers free medical screenings to former Iowa AEC/DOE workers from IAAAP and Ames Laboratory (another DOE site in Ames, Iowa that was established in the 1940s to produce high-purity uranium metal for atomic energy). Medical screening services are offered to former employees who may be at-risk for health conditions as a result of exposure to hazardous or radioactive substances during their employment at a DOE facility. If workers are found to have an occupational illness, they are encouraged to file a claim with the Department of Labor Energy Employees Occupational Illness Compensation Program (EEOICP).

The eventual inclusion of the IAAAP data into the Comprehensive Epidemiologic Data Resource (CEDR) will allow other researchers to pool the data or serve as a reference population for other cohorts (e.g., Pantex). Pooling data is problematic unless well-documented, site-specific studies are performed that allow for an estimate of socioeconomic status, a requirement for inclusion into the database. Finally, this study will also fulfill requests from the community, as well as the workers, for a site-specific mortality and cancer incidence study.

<div align="center">Specific Aims</div>

The main objective of this study is to examine mortality and cancer incidence in the cohort of former AEC workers at the Iowa Army Ammunitions Plant. It is hypothesized that former atomic weapons workers are at increased risk of death and cancer due to exposure to carcinogens and other toxicants in the workplace.

Specific Aim # 1: Compare the overall mortality rates for the former IAAAP AEC worker population as compared to reference populations.

- Determine if the overall mortality rate is higher in the IAAAP AEC workers as compared to either the mortality rates for the U.S. population or state of Iowa.

Specific Aim #2: Determine if cause-specific mortality rates are higher in the IAAAP AEC workers as compared to the cause-specific mortality rates for the U.S. population or state of Iowa.

- Determine whether there is excess mortality in the cohort for causes of death known to be associated with smoking.

Specific Aim #3: Determine whether former IAAAP AEC workers who are residing in Iowa experience higher site-specific cancer incidence rates as compared to a reference population from the state of Iowa.

- Do IAAAP AEC workers experience higher overall cancer incidence rates or *a priori* defined site-specific cancer rates when compared to a reference population from the Iowa catchment area.

<div align="center">Justification for Specified Outcomes</div>

The particular outcomes of interest for the mortality and cancer incidence portions of the study follow from extensive review of other retrospective mortality studies of nuclear workers. The *a priori* defined cause-specific causes of mortality include: heart disease, liver disease, kidney disease, anemia and bone marrow failure, interstitial lung disease, cancer of the larynx, lung cancer, bronchus, as well as cancer of the oral cavity, cancer of the pharynx, cancer of the trachea, sinus cancer, liver (hepatocellular and hepatobiliary) cancer, and leukemia. The *a priori* selection of site specific cancers is based on known carcinogenic potential of radionuclides (alpha, beta/gamma) from high-dose cancer mortality studies. The sites of cancer follow distribution patterns of radionuclides within the body: lung, liver, head-sinus carcinomas, leukemias and bone sarcomas (BEIR VII, 2005). Finally, mesothelioma is another site of interest due to asbestos exposure during construction activities performed at the plant.

Cardiovascular Disease

The *a priori* selection of heart and kidney disease is based on a history of excess mortality from ischemic heart disease found among workers exposed to 2,4- and 2,6-dinitrotoluene (DNT) (Levine et al., 1986). Nitrates are potent vasodilators and have been associated with withdrawal angina, coronary infarction and sudden death (Carmichael and Lieben, 1963). A retrospective cohort mortality study with 5529 nitroglycerin, 4989 dinitrotoluene, and 5136 unexposed workers comparing the mortality of the exposed groups with that of the United States population and that of the unexposed group with life-table analysis did not show an increased cardiovascular risk (Stayner et al., 1992). A significant interaction between age and nitroglycerin exposure was detected for ischemic heart disease in younger workers (SRR 3.30 for workers under 45 and SRR 5.46 for workers under 35) (Stayner et al., 1992).

Liver Disease

TNT is associated with liver toxicity when workers are exposed to amounts close to accepted Threshold Limit Values (TLV). Liver damage has been documented in TNT workers both in the U.S. and China (Morton et al., 1977 and Li et al., 1991). In addition, an excess of hepatobiliary cancer (SMR=2.7, 95% CI 0.98-5.83) was found in a NIOSH study of 4,989 exposed and 7,436 unexposed workers (Stayner et al., 1993).

Respiratory Disease

The selection of interstitial lung disease (includes asbestosis and beryllium disease) is included because of reported use of asbestos in the early years of production. Former IAAAP workers also reported beryllium exposures after sanding and grinding of beryllium alloy tools (Fuortes, 2001). Sites participating in the DOE medical screening programs have reported increased beryllium sensitization (BeS) (Viet et al. 2000, Welch et al. 2004, and Rodrigues et al., 2008). Of the 1,786 former workers at the Nevada Test Site (NTS), 23 had a confirmed positive beryllium sensitization by blood beryllium

lymphocyte proliferation test (BeLPT) (Rodrigues et al. 2008). At the NTS, the workers with evidence of BeS were those who performed cleanup and those who worked in a specific building where beryllium parts were machined. Screening for BeS among construction trade workers at Hanford Nuclear Reservation, Oak Ridge Reservation and the Savannah River Site demonstrated an increased risk to be associated with ever working in a site building where beryllium activities had taken place (Welch et al., 2004). Additionally, a case-control study performed at Rocky Flats Nuclear Reservation found that years of employment, an estimate of cumulative exposure, was greater in workers with chronic beryllium disease (Viet et al., 2000).

Construction workers at multiple DOE sites have also been exposed to asbestos containing materials and have reported increased asbestosis and pulmonary abnormalities (Makie et al., 2005 and Dement et al., 2009). A large excess of asbestosis (SMR=33.89, 95% CI 18.03-57.95) and mesothelioma (SMR=5.93, 95% CI 2.56-11.68) in the combined cohort of DOE construction workers support an asbestos exposure etiology (Dement et al., 2009).

A detailed review of the specific malignant outcomes of interest is covered in the following sections.

Malignancies of the Respiratory Tract and Pleura

Cancers of the respiratory tract and pleura include lung, sinonasal and nasopharyngeal cancers. In the United States, lung cancer is the leading cause of death in both men and women. The incidence and mortality rates of lung cancer are nearly equivalent so vital statistics provide an accurate record of occurrence (Alberg and Samet, 2003). About 90% of lung cancer is classified into four major histologic types: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell undifferentiated carcinoma. Currently, adenocarcinoma is the most common type. While tobacco smoking has been proven to be the predominant cause, there are other risk factors as well.

One of the first occupational carcinogens to be discovered was radon in underground miners (Samet, 1989). Early studies attributed the percentage of lung cancer due to occupational exposures as high as 15% of male lung cancer and 5% of female lung cancer (Doll and Peto, 1981). Pooled data from five American case-control studies spanning a wide-range of industrial occupations suggested that up to 17% of lung cancers were due to well-known carcinogens (Vineas et al., 1988). The list of human occupational causes of lung cancer also includes arsenic, asbestos, chromates, chloromethyl esters, ionizing radiation, nickel, polycyclic aromatic hydrocarbons, radon progeny, and other agents (Coultas and Samet, 1992). Exposures considered as probable lung carcinogens are beryllium, cadmium, man-made vitreous fibers and ambient air pollution. There are also numerous complex interactions between the risk factors for lung cancer (i.e. tobacco smoking with asbestos or radon). Typically, tobacco smoking potentiates the effect of many known occupational lung carcinogens (Saracci and Boffetta, 1994). A recent study of the atomic bomb survivors shows that smoking a light to moderate amount of cigarettes per day has a super-multiplicative effect on risk of lung cancer in men (Furukawa et al., 2010).

Epidemiologic studies of populations exposed to acute, high doses of radiation clearly demonstrate that lung cancer is associated with exposure to ionizing radiation. Studies of atomic bomb survivors show the results of both the immediate and delayed effects of acute, whole-body exposure (Shimizu, 1990). The estimated relative risk for lung cancer was significant at $ERR_{1\,SV} = .95$ (Thompson, 1994). In follow-up studies, there was a significant dose-response association with lung cancer and radiation dose (Preston et al., 2007). The results of the high-dose studies may not address the risks experienced by nuclear energy workers who were generally exposed to chronic, intermittent low-dose radiation. Moreover, the Japanese population differs from occupational groups in other fundamental ways. The cancer risk among survivors was

influenced by thermal or blast effects, malnutrition, sanitary conditions, infectious diseases and other health conditions (Boice, 1990).

There are two types of radiation associated with developing lung cancer: low linear energy transfer (LET) radiation (i.e. gamma rays and x-rays) and high-LET radiation (i.e. neutrons and alpha particles). Ionizing radiation injures living cells in biologic tissue by depositing enough localized energy to cells to disrupt the atoms and molecules on which it impacts. Subsequently, these collisions may produce ions and free radicals that lead to tissue injury.

Radon, a high-LET type of radiation, is an inert gas that is produced naturally from radium in the decay pathway of uranium. Radon emits alpha (α) particles that can damage the DNA of cells of the respiratory epithelium (Alberg, 2003). Underground miners of uranium and other ores have established exposures to radon decay products as a cause of lung cancer (Lubin, 1995). Radon is an indoor air pollutant as well since it enters buildings and homes through soil, gas and water. It is estimated that 15,000-22,000 lung cancer deaths per year in the U.S. are caused by radon exposure (NRC, 2006).

Plutonium workers at the Mayak plant in the Russian Federation were also exposed to alpha particle radiation and lung cancer mortality was examined. While it was difficult to separate the effects of low and high- LET type of radiation, researchers demonstrated an estimated excess relative risk per unit dose equivalent in the lung due to the plutonium alpha particles (at age 60) to be 0.6/Sv (Kreisheimer et al., 2000).

Exposure to low-LET radiation from x-rays, beta particles and gamma rays has been associated with lung cancer. The three principle populations studied are atomic bomb survivors, patients receiving medical radiation for treatment and occupation cohorts. While the single, high-dose exposure of the atomic bomb survivors was associated with lung cancer, the intermittent low doses received by tuberculosis patients from diagnostic imaging was not significant (Howe, 1995). In the largest cohort of

nuclear industry workers, the 15-country study, the rate of all solid cancers was elevated (Cardis et al., 2007). The results suggest that there is a small excess risk of cancer even to low doses and dose rates of externally penetrating radiation.

Other potential occupationally-related cancers of the upper respiratory tract include sinonasal, nasopharyngeal and laryngeal cancers. Sinonasal cancers are very rare and have been linked to nickel (Sunderman et al, 1989), wood dust (Gordon et al., 1998), formaldehyde (Luce et al., 1993), cutting oils (Luc, 2002) and chromium exposure (Hernberg et al., 1983). Cancers in nickel workers have occurred most frequently in the nose and ethmoid sinuses and usually are of squamous histology (Sunderman et al., 1989).

Laryngeal cancer is more common, approximately 2% of the U.S. cancer incidence, and has been primarily linked to asbestos, human papillomavirus, alcohol and tobacco smoking along with the above mentioned risk factors for sinonasal cancers. It is the second most common respiratory cancer after lung cancer and is primarily found in male blue collar workers. Chronic consumption of alcohol along with tobacco smoking independently increases the risk of laryngeal cancer in a dose-dependent manner (Maier, 1997).

<center>Mesothelioma</center>

Mesothelioma is a rare cancer usually associated with chronic asbestos exposure. It is an aggressive tumor of serosal surfaces, such as the pleura and peritoneum (Robinson and Lake, 2005). This neoplasm arises from the mesothelial lining the pleura. About 80% of patients diagnosed with malignant pleural mesothelioma have a history of asbestos exposure (Cugell and Kamp, 2004). There is typically a 20-50 year latency between asbestos exposure and development of the malignancy, usually presenting in the 6th through 8th decades (Ismail-Khan et al., 2005). This tumor was once considered very rare but the incidence has been increasing. In the United States malignant mesothelioma

occurs in approximately 2,500 persons per year and 80% are men (Ismail-Khan et al., 2005). The disease typically presents as progressive dyspnea and persistent chest wall pain.

Malignancies of the Liver and Gastrointestinal Tract

Cancer of the liver is the fifth most common cancer in the world. Most of the primary liver cancers are of epithelial cell origin, and are classified into six major histological types. Among cancers involving hepatocytes, hepatocellular carcinoma (HCC) is the most common type worldwide (Fritz, 2000). The male to female ratio is approximately 4:1 and incidence of HCC is increasing in developed countries (McGlynn et al., 2001). HCC has been associated with chronic infection with hepatitis B and C viruses, alcohol-induced liver injury, aflatoxin (a fungal toxin found in peanuts and corn), tobacco smoking, genetic disorders leading to liver injury (i.e. hemochromatosis), and occupational exposures (Bosch et al., 2004). Moreover, liver cancer has been elevated in studies evaluating incidence in the atomic bomb survivor studies (Thompson et al., 1994). Survivors were exposed to low-LET gamma radiation and neutrons. Excess risk was particularly high among males and among those exposed to radiation in their teens and twenties (Cologne et al., 1999).

Other recent studies have shown similar results. Occupational liver cancer mortality risks were evaluated in 11,000 workers at the Mayak nuclear facility in the Russian Federation. Many of the workers were exposed to high levels of inhaled plutonium and high doses external gamma radiation that were substantially higher than current occupational dose limits (Gilbert et al., 2000). Comparisons with Russian liver cancer incidence rates indicated an excess risk, especially among those with detectable plutonium body burdens and among female workers in the plant. Comparisons within the worker cohort, which evaluated the role of plutonium body burden with adjustment for

cumulative external dose, indicated an excess risk among workers with burdens estimated to exceed 7.4 kBq (relative risk 17, 95% CI 8-36) (Gilbert et al., 2000).

Another alpha-emitter, Thorotrast (thorium dioxide), has been linked to liver cancer, primarily hemangiosarcoma. Thorotrast was used as a radiographic contrast agent from 1930 to 1955 in Europe, North America and Japan. In Denmark, a study reported on 1,000 Thorotrast-exposed patients who received intra-arterial injection of the material for cerebral arteriography were followed (Andersson and Storm, 1992). Thorotrast injection has shown excessive risks for primary liver cancer and leukemia, with significant dose-response relationships; and increased risk for cancers of the gallbladder and extrahepatic bile ducts (Andersson and Storm, 1992).

Epidemiological evidence also links primary liver cancer to certain chemicals. The hepatocarcinogenic effects of vinyl chloride was first detected in experimental animals and confirmed in human studies (Wogan, 2000). Specifically, liver hemangiosarcoma has been associated with vinyl chloride monomer exposure (Blair and Kazerouni, 1997). In a large cohort of 10,173 workers from 37 U.S. plants, workers who were exposed to vinyl chloride for at least one year had significant mortality from angiosarcoma (15 deaths), cancer of the liver and biliary tract (SMR 6.4, 95% CI 4.5 to 8.8), and cancer of the brain and emphysema/chronic obstructive pulmonary disease (Wong et al., 1991).

<center>Malignancies of Bone</center>

Osteosarcoma is the most common primary bone tumor that occurs most frequently in adolescents, but there is a second peak of frequency among adults greater than 60 years. It is a rare cancer that represents about 1% of all cancers diagnosed in the United States and is more common in males (Mirabello at al., 2009). The only environmental agent proven to cause osteosarcoma is ionizing radiation (Picci, 2007). Bone cancers were first recognized in women working as radium dial painters before

1930. Small amounts of radium salts were added to paint to make it fluorescent. The greatest risk of internal exposure to radium occurred through "tipping" or "pointing" the brush between the lips, thus ingesting small amounts of ionizing radiation (Fry, 1998). Two radium isotopes ^{226}Ra and ^{228}Ra are associated with osteosarcoma and carcinomas involving the paranasal sinuses (Rowland et al. 1978). Average doses estimated from ingesting radium ranged from 0.8 to 12 Gy, and bone cancers were documented more than 60 years after initial exposure (UNSCEAR, 2000).

Bone cancers have also been described in Mayak workers exposed to high levels of plutonium. Internal comparisons by level of exposure showed an increase risk of cancer with increasing estimated body burden. Most of the cancers occurred 20 years after the initial date of hire and excess mortality was demonstrated in workers with body burdens estimated to exceed 7.4 kBq (RR 7.9, 95% CI 1.6-32.0) (Koshurnikova et al., 2000). External radiation exposure was not significantly associated with bone cancers in the atomic bomb survivor studies or Mayak cohort studies.

Malignancies of the Lymphohematopoietic System

Lymphohematopoietic (LH) malignancies are a heterogeneous group of neoplasms that arise from the clonal malignant transformation of various cell lines of the blood and lymphoid tissues. All LH malignancies combined account for about 8% of the cancer incidence documented annually in the U.S (Ries et al., 2001). Generally, the LH malignancies are delineated into leukemia and lymphomas. There are two types of leukemia, lymphocytic and myelogenous, and each has acute and chronic forms. Leukemia is a hematopoietic stem cell disorder characterized by a block in differentiation of hematopoiesis, resulting in growth of a clonal population of neoplastic cells or blasts (Shipley and Butera, 2009). Acute lymphoblastic leukemia (ALL) is the predominant acute leukemia of childhood. AML is the most common acute form, yet continues to have the poorest survival. The incidence of acute myeloid leukemia (AML) increases

with age. Chronic lymphocytic leukemia (CLL) is the most common leukemia, with a median age at presentation of 65-70 years old, and more commonly seen in males (Rosenstock et al., 2005). Nearly 50% of patients with CLL are asymptomatic at presentation with the diagnosis made incidentally following a routine blood count (Linet et al., 2007).

The solid tumors of the LH malignancies, also referred to as the B-cell immunoproliferative disorders, include multiple myeloma (MM), Hodgkin lymphoma (HL), and non-Hodgkin lymphoma (NHL). NHL is the most common type of lymphoma in Western countries, accounting for about 30% of new diagnoses (Armitage and Weisenburger, 1998).

The development of malignancies of the LH system has been associated with multiple risk factors. These include age, genetic disorders, antecedent hematologic disease, ionizing radiation, chemical exposures, agricultural work, tobacco smoking, and previous chemotherapy (Rosenstock et al., 2005). Chronic exposure to certain chemicals shows an increase risk of leukemia, specifically benzene exposure in rubber, refinery and chemical workers. Benzene is present in crude oil and is involved in most stages of the production of petroleum. While most studies have linked chronic benzene exposure to the development of AML (Savitz and Andrews, 1997), emerging studies are showing an association with CLL as well (Glass et al., 2003).

Specific substances in cigarette tobacco smoke are known to be leukemogenic, including benzene, various acids, and agricultural chemicals. Smoking tobacco has been consistently associated with risk of all leukemias combined, especially AML (Linet et al., 1991).

Ionizing radiation is a well-established risk factor for LH malignancies. Among survivors of the atomic bomb studies, an increased incidence of AML was observed with a peak at 5-7 years after exposure (Preston, 1994). There was strong evidence of

radiation-induced risks for all subtypes except CLL, and there were significant subtype differences with respect to the effects of age at exposure and gender.

Using the U.S. population as reference, a mortality study of workers exposed to alpha-radiation at the nuclear production plant in Oak Ridge, Tennessee showed white male workers had a higher risk of death for all cancers of the lymphopoietic system (SMR 1.46, 95% CI 0.92-2.22)(Loomis and Wolf, 1996).

Therapeutic radiation has been found to increase the risk of secondary AML (Kossman, 2000). Patients who received radiation to treat ankylosing spondylitis have reported elevated risks of CLL, although not all studies have shown a dose-response relationship (Wick et al., 1999). A non-significant dose-response relationship was demonstrated for CLL in radiation workers from the Rocketdyne plant (Boice et al., 2006), but no association was found in the 15-Country Collaborative Study of Cancer Risk (Cardis et al., 2007).

In studies examining associations between cancer and radon progeny in uranium miners, elevated mortality rates were observed for MM and NHL, but not CLL (Schubauer-Berigan et al., 2009). However, a larger case-cohort study of CLL incidence in Czech miners found a positive association with cumulative radon exposure (Rericha et al., 2006).

Malignancies of the Thyroid Gland

Thyroid malignancies are an uncommon form of cancer overall, but some evidence suggests the overall incidence is increasing, from 3.6 per 100,000 in 1973 to 8.73 per 100,000 in 2002, a significant 2.4 fold increase (Daves and Welch, 2006). Despite the increasing incidence, mortality rates have remained stable. It has been theorized that this increase is mostly due to diagnostic scrutiny or changes in diagnostic criteria. This increase has sparked interest and concern about the potential hazards of environmental and occupational exposures. Known risk factors include ionizing

radiation, genetics, benign thyroid disease, certain medications known to stimulate the thyroid, weight gain, and dietary iodine (both deficiency and excess) (Ron, 1996).

The most common risk to the thyroid gland involves prior head or neck treatment with external beam radiation for certain childhood illnesses. Therapeutic radiation (external gamma radiation) in childhood was performed specifically for presumed enlargement of the thymus gland, facial acne, tonsillar enlargement, fungal infections of the scalp (tinea capitis) and various infections of the cervical lymph nodes (Schneider 1997). Several retrospective analysis indicated that adults with a history of childhood exposure had a high prevalence of thyroid nodules and malignancies (typically, papillary and follicular thyroid carcinomas) (Schneider et al., 1986 and Shore et al., 1993). The thyroid gland in children has one of the highest risk coefficients of any organ and is the only tissue for evidence for risk as low as 0.10 Gy (Lubin, 1995).

Radioactive iodine, ^{131}I, has been used to treat Graves' hyperthyroidism. The most recent investigation of the risk of thyroid malignancies following ^{131}I for hyperthyroidism involved a population-based cohort of 7,400 patients treated between 1950 and 1991. Overall cancer incidence and mortality was decreased, however thyroid cancer incidence (SIR 3.25, 95% CI 1.69-6.25) and mortality (SMR 2.78, 95% CI 1.16-6.67) were increased (Franklyn et al., 1999).

There have been marked increases in childhood thyroid cancer due to exposure to ^{131}I after the 1986 accident at the Chernobyl power station near Kiev in the Ukraine. There was an increase in thyroid carcinoma in nearby Belarus, Ukraine and the Russian Federation as a consequence of ^{131}I fallout. Subjects who were younger at the time of exposure, generally less than 5 years old, had a greater risk of developing a more aggressive form of carcinoma (Pacini et al., 1997).

Finally, the atomic bomb survivor studies have shown an increase risk of thyroid cancers as well. An excess relative risk of 1.15/Sv was reported (Thompson, 1994).

Malignancies of the Urogenital Tract

Bladder cancer is the most common malignancy of the urogenital tract and has been linked to multiple environmental and occupational exposures. Bladder cancer is the fourth most common malignancy of men living in developed countries, and the median age of diagnosis is 65 to 70 years (Kirkalli, 2005). Known risk factors for bladder cancer are tobacco smoking, infections, industrial chemicals, genetics and ionizing radiation. Tobacco smoking accounts for almost half of all bladder cancer in men and about 37% among women; overall, smokers have twice the risk of nonsmokers (ACS, 2001).

Occupational studies have illustrated risks to workers in the textile, printing, plastic, rubber, leather, and cable industries and have been exposed to a variety of toxicants: dyes, rubber, tar and metals. Exposure to β-naphthylamine, 4-aminobiphenyl (ABP), and benzidine, principally among workers in the textile dye and rubber tire industries, are a few of the agents unequivocally associated with bladder cancer and are now banned from the workplace (Kirkalli, 2005). There are other carcinogens still in the workplace that are potentially high risk; orthotoluidine, aromatic amines, polychlorinated biphenyls, formaldehyde, asbestos, diesel exhaust, and solvents (benzene, dioxane, and methylene chloride) (Steenland and Palu 1999, and Kogevinas et al., 2003).

Ionizing radiation and chemotherapy increase the risk of bladder cancer. Women who were treated for ovarian cancer with radiotherapy and/or chemotherapy had higher rates than women who were treated with surgical resection only (Kaldor, 1995). Finally, in the atomic bomb survivor studies, incidence of bladder cancer demonstrated an estimated relative risk of $ERR_{1SV} = 1.02$ (Thompson, 1994).

Other malignancies of the urogenital tract include renal cell carcinoma (RCC), a rare cancer accounting for only 3% of cancers diagnosed in the U.S. Evidence suggests the etiology is also related to genetic, occupational and environmental risk factors. Up to one-half of patients with von Hippel-Lindau disease develop RCC (Christenson, 1982). Other risk factors include smoking, obesity, nephrolithiasis, and chronic use of

phenacetin (McCredie et al., 1988). Several industrial chemicals, such as polyaromatic hydrocarbons (PAHs), have been associated with RCC. The combustion of petroleum coke and coal tar pitch produces volatile agents containing PAHs. Exposed men who were employed between 1950 and 1955 at one of ten petroleum coke plants had a significant relative risk of 7.5 for RCC (Redmond et al., 1972). Other industrial chemicals include, organic solvents, polychlorinated biphenyls, and possibly trichloroethylene and hydrazine-based fuels.

Certain metals have been implicated as nephrotoxins as well: cadmium, lead, steel, aluminum, ferrosilicon and uranium. There have been two studies that have observed an increased risk of RCC in workers processing uranium (Dupree-Ellis et al., 2000 and Fraser et al., 1993). One of these studies, performed at Mallinckrodt Chemical Works, showed that while the excess relative risk of RCC was based on a small number of cases, there was a significant dose-response relationship (with external radiation) (Dupree-Ellis et al., 2000). The authors conceded that this excess risk may be due to internal radiation or chemical exposures not accounted for.

Finally, asbestos exposure has been linked to RCC because toxicologic experiments with asbestos exposure have shown that fibers may reach the kidney through the blood or lymphatic systems and have been found in urine. In a study of 17,000 insulators exposed to asbestos, a statistically significant SMR of 2.22 for RCC was demonstrated (Selikoff et al., 1979).

<center>Malignancies of the Central Nervous System</center>

Of tumors of the central nervous system, brain neoplasms are the most common. Approximately 11 to 12 per 100,000 persons in the U.S. are diagnosed with a primary brain tumor each year, and 6 to 7 per 100,000 are diagnosed with a primary malignant brain tumor (Wrensch et al., 2002). Gliomas and other neuroepithelial tumors account

for 49% of primary malignant tumors (Legler et al., 1999). Meningiomas are the most common non-malignant brain tumor.

Among adults, incidence of brain cancer peaks between the ages of 65 and 75 and is more common in white men (Reis et al., 2001). The tumors are very heterogeneous histologically so the nature and magnitude of the risk factors for primary tumors have varied by study (Wrensch et al., 2002). Probable risk factors for malignant brain tumors include: vinyl chloride, formaldehyde, lead, organic solvents, ionizing radiation, agricultural work, head trauma, familial diseases (neurofibromatosis), and genetics (Rosenstock et al., 2005). The strongest evidence to date for an increased risk of meningioma is exposure to ionizing radiation. Studies of ionizing radiation have focused on the atomic bomb survivors and patients with exposures in medical and occupational settings (Barnholtz-Sloan and Kruchko, 2007).

Therapeutic radiation shows strong risk for brain tumors. In a pooled analysis of 28,008 infants treated for skin hemangiomas, results showed a significantly elevated excess relative risk of 4.5 ERR/Gy if the treatment was given before 5 months of age (Karlsson et al., 1998). Infants who were exposed at younger ages had a higher risk than those exposed after 5 months of age. Similarly, children treated for ALL showed a relative risk of 21.7 for subsequent development of a CNS tumor (Neglia et al., 1991).

High rates of brain cancer have also been observed among employees who worked at plants producing nuclear fuel and weapons. Exposures to cumulative doses of 5 rem or less were examined. The large cohort of 140,000 U.S. white males (with approximately 3.8 million person-years of observation) demonstrated a 25-30% increased risk of brain tumor (Alexander and DiMarco, 2001).

Similarly, a mortality study of workers at the nuclear production plant in Oak Ridge, Tennessee showed white male workers had a higher risk of death for cancer of the brain and other CNS (SMR 1.28, 95% CI 0.76-2.02) (Loomis and Wolf, 1996).

Finally, survivors who were within 2.0 km of the hypocenter of the atomic bomb explosion in Hiroshima showed an increased risk of meningioma. The incidences of meningioma classified by distances from the hypocenter of 1.5-2 km, 1.0-1.5 and less than 1.0 km were 6.3, 7.6 and 20.0, respectively (Shintani et al., 1999). There was also a significant correlation between the incidence and the radiation dose. The incidences of meningioma classified by doses to the brain of 0.099 Sv, 0.1-0.99 Sv and more than 1.0 Sv were 7.7, 9.2 and 18.3, respectively (Shintani et al., 1999).

Organic solvents are considered a possible brain carcinogen because they are exposures common to several occupational groups identified as being at higher risk. Chlorinated aliphatic hydrocarbons pass through the blood-brain barrier because of their high solubility in fats (Sato and Nakajima, 1979). Exposure to methylene chloride, carbon tetrachloride, tetrachloroethylene, and trichloroethylene assessed through a job exposure matrix showed a higher risk of astrocytic brain cancers (Heineman et al., 1994). The strongest association was noted for methylene chloride, for which relative risks increased with duration of employment and average intensity of exposure (Heineman at al., 1994).

Malignancies of the Skin

The most frequently occurring skin cancers known to be of environmental and occupational origin are the non-melanoma skin cancers, which include basal cell and squamous cell carcinomas. The incidence of such cancers is difficult to ascertain because they are usually treated in an outpatient setting (Glass and Hoover, 1989). Non-melanoma skin cancers are the most common malignancies in the United States, and the incidence is increasing (Christenson et al., 2005). Basal cell carcinoma represents about 75% of all cutaneous neoplasms and is more frequently diagnosed in men over 50 years old. Recent evidence demonstrates a marked rise in incidence of non-melanoma skin cancer in persons under 40 years old, especially women (Christenson et al., 2005).

Overall lifetime risk of developing a non-melanoma skin cancer was estimated to be 28-33% for basal cell carcinoma and 7-11% for squamous cell carcinoma (Miller and Weinstock, 1994).

Malignant melanoma is less common but more serious form of skin cancer, accounting for about 75% of overall mortality (Hall et al., 1999). Incidence and mortality rates are also increasing worldwide, but survival has been improving (Liu and Soong, 1996). In recent years, however, rates for most age-sex groups appeared to stabilize or decline, possibly due to greater public education on minimizing sun exposure and tanning bed use.

The increasing incidence of skin cancer overall is likely due to multiple factors, including increased surveillance, increased longevity of the general population, increased exposure to ultraviolet (UV) radiation, and ozone depletion (Christenson et al., 2005). Known risk factors for non-melanoma skin cancers include a particular phenotype of appearance (fair complexion, blond/red hair, blue eyes, childhood freckling, inability to tan and skin sensitivity to sun). Malignant melanoma is associated with fair complexion as well, but is more closely related to intermittent, intense UV radiation exposure in childhood and adolescence (Armstrong and Kricker, 2001).

Low-dose ionizing radiation has been associated with non-melanoma skin cancers, particularly basal cell carcinomas (Lichter et al., 2000). The use of x-rays for tinea capitis, facial acne, hypertrichosis, hemangioma, lupus vulgaris, toxic goiters and eczema has been associated with the development of skin cancer (Lichter at al., 2000 and Shore, 2001). In several studies, elevated risks in relation to therapeutic radiation were found to be confined to the site of radiation exposure and have significantly elevated odds ratios of up to 5.7 for basal cell carcinoma and up to 4.8 for squamous cell carcinoma (Lichter et al., 2000). Similarly, there was a strong positive dose response association for basal cell carcinoma in a study evaluating cancers of the atomic bomb survivors (Ron et

al.1998). The cases identified in the Hiroshima and Nagasaki tumor registries were exposed to about one to four sieverts of ionizing radiation.

Occupational risk factors for skin cancer include exposure to asphalt, tar, soot, crude paraffin, anthracene, pitch, organic and non-organic solvents, mineral oils, organophosphate compounds, inorganic arsenic, fiberglass dust and dry cleaning agents (Narbutt et al., 2005). Inorganic arsenic is unique in that skin tumors may be produced by ingestion, injection and inhalation in humans (Pershagen, 1981). In southwestern Taiwan, the concentration of arsenic in the drinking water was a high as 1220 µg/l (Tseng et al., 1968). There was a dose-dependent relationship between the arsenic level in the water and prevalence of skin cancers (Tseng et al., 1968). Regardless of the route of exposure, chronic arsenic poisoning causes hyperpigmentation, hyperkeratosis, and nonmelanoma skin cancers. The non-melanoma skin cancers attributed to arsenic exposure are multiple, aggressive, and occur at sites not directly exposed to UV radiation (Shannon and Strayer, 1989).

A study of 5,100 workers at the Lawrence Livermore National Laboratory in California, a high-technology, high-energy physics research facility, demonstrated excess incidence of melanoma (Reynolds and Austin, 1985). The indicators of occupational risk from this study were further investigated in a small case-control interview study using multivariate analysis. Several occupational indicators of risk were tested including: employment as a chemist, potential exposures from volatile photographic chemicals, fumes from high explosives, ionizing radiation, workplace experience at the off-site non-nuclear weapons testing facility, and/or the atmospheric nuclear testing site (Austin and Reynolds, 1997). After adjustment for constitutional and occupational risk factors of interest, the odds ratio associated with reported work around sources of ionizing radiation remained elevated (OR 2.3, 95% CI 1.0–7.6) (Austin and Reynolds, 1997).

Exposures of Interest

Former AEC/DOE workers were potentially exposed to a variety of exposures including, beryllium, industrial chemicals, ionizing radiation, heat, noise and physical stressors. Of primary interest is exposure to ionizing radiation. Early AEC/DOE workers were potentially exposed to high levels of both internal and external radiation before adequate safety and control measures were implemented. The following section reviews potential exposures experienced by the Line 1 workers.

Ionizing Radiation

Ionizing radiation is composed of high-energy sub-atomic particles that have sufficient energy to break atomic bonds in absorbing materials, such as biologic tissues. Damage occurs at the cellular level by damaging DNA and causing mutation and chromosomal changes. Ionizing radiation may also lead to cell transformation (a stage in cancer development) and cell death (UNSCEAR, 2000). After ionizing radiation exposure, cells may lose the ability to recover from the assault. The damage may arrest in the cell cycle, possible the damage-limitation step, where cells repair and reduce the consequences of a given dose (UNSCEAR, 2000). There are two forms of ionizing radiation; electromagnetic radiation and particulate radiation. The high-energy electromagnetic radiation includes x-rays and gamma rays, while the particulate radiations include electrons, protons, neutrons, alpha particles or other subatomic particles (BEIR VII, 2005). Radiation is usually measured in dose units called grays (Gy) or sieverts (Sv), which are measures of energy deposited in living tissue (see Table 1.2 for common, equivalent units of radiation dose). For this review, radiation units are reported in the units (i.e., International units or special units) to maintain consistency with the original article.

X-rays and gamma rays are sparsely ionizing and produce fast electrons which cause only a few dozen ionizations as they traverse a cell (BEIR VII, 2005). The rate of

energy transfer is called low-linear energy transfer (LET). The heavier particulate

radiations, i.e. alpha particles, transfer more energy per unit length as they traverse the

cell (high-LET). Because high-LET radiations cause more damage per unit absorbed

dose, a weighted quantity, *equivalent dose*, or its average over all organs, *effective dose*,

is used for radiation protection purposes (BEIR VII, 2005). For low-LET radiation,

equivalent dose equals the *absorbed dose*. For high-LET radiation, the *equivalent dose*

equals the *absorbed dose* multiplied by a weighting factor (Q-factor) to account for their

increased effectiveness (BEIR VII, 2005). Internationally, the sievert (SV) is the official

unit of dose equivalent. Since the radiation weighting factor is dimensionless, the base

units of Sv remain in joules per kilogram (1 Sv = 1 J/ Kg). A Sv of *equivalent dose* is

defined as the dose in Gy multiplied by the weighting factor (Q-factor), for the type of

radiation. For low-LET radiation the *absorbed dose* in Gy equals the biologically

effective dose in Sv. For high-LET radiation, such as alpha particles (Q-factor equals 20),

1 Gy will deliver an effective dose of 20 Sv to biologic tissue. See Table 1.3 for review of

types of radiation and weighting factors.

Ionizing radiation is emitted from both natural and artificial sources. The main

sources of natural ionizing radiation are: (1) cosmic radiations, which originate from

outer space (mostly simple protons), (2) terrestrial radiations, which emanate from

radium, thorium, uranium, and other radioactive elements in earth's crust, and (3) internal

radiations, which are emitted by potassium-40, carbon-14, and other radioactive isotopes

normally contained in living tissues (Rosenstock et al. 2005). A significant source of

natural exposure is due to radon gas which emanates from soil and water. Radon gas

from natural source may accumulate in building, especially in confined areas such as

basements.

Overall, the worldwide average background ionizing radiation dose for a human is

about 2.4 mSv per year (UNSCEAR, 2000). Ionizing radiations from natural and

artificial sources are identical in composition and effects. The medical use of radiation is

the largest growing source of artificial radiation. Artificial sources of radiation include x-ray machines, computed tomography (CT scanners), particle accelerators, and nuclear reactors. See Table 1.4 for characteristics of commonly encountered radionuclides.

Radiation exposure also occurs as a result of occupational exposures. The average yearly occupational dose equivalent of whole-body radiation is less than 1 mSv (Kahn et al. 1983). Historically, occupational groups with high radiation exposures were radiologists, airline pilots and crews, uranium miners, petroleum refinery workers, luminous dial painters, nuclear reactor operators, and astronauts (Kahn et al., 1983). Because of radiation protection programs, the average annual doses to radiation workers have declined steadily. Currently, most workers receive doses that are less than or near the power detection limits of personal dosimeters.

At IAAAP, AEC/DOE workers reported exposures to radiation through a wide variety of job titles (Fuortes, 2001). Information concerning the early history of IAAP nuclear weapons assembly activities still involves classified information and, therefore, a clear description of events at that time is not publicly available. The primary work activity involving external radiation exposure involved testing nuclear components using DU, handling sealed nuclear components called pits containing enriched uranium or plutonium, and industrial radiography operations (Leonowich et al., 2004). Based on the Burlington dosimetry records received from the Pantex plant, it appears that about 500 of the workers who had the greatest potential for exposure were provided dosimeters. Most of these records demonstrate exposures well within the accepted limits, see Table 1.5. Radiation data available from the plant demonstrate that most monitored workers were exposed to 0-1 rem of external radiation (Leonowich et al., 2004). Former workers have voiced concerns though about past exposures because many of the production workers may not have been properly monitored. There are individual reports of workers who were assigned badges but may not have routinely worn them. Some of the dosimeter badges may have been left in their lockers or on a main storage board (Fuortes, 2001).

Additionally, many of the security personnel stated that even though they worked around the radioactive materials, they did not wear dosimeters.

Depleted Uranium

Depleted uranium (DU) is a silver-white, lustrous, dense, slightly radioactive element. It is a heavy metal and is twice as dense as lead. Natural uranium consists of a mixture of three radioactive isotopes: U-238 (about 99.27% by mass), U-235 (about 0.72%), and U-234 (about 0.0054%) (ATSDR, 2003). Uranium is present throughout the natural environment and contributes to a natural level of background radiation.

DU is a byproduct of the process by which uranium is enriched to produce nuclear reactor fuel and nuclear weapons components. The DU leftover is about 40% less radioactive than natural uranium. The DU remaining after removal of the enriched fraction is comprised of about 99.8 % U-238, 0.2% U-235, and 0.0006% U-234 by mass (ATSDR, 2003). Reprocessing the uranium in spent nuclear fuel may result in DU containing very small amounts of U-236, plutonium, americium, neptunium, fission products including cesium-137 and technetium-99 (ATSDR 2003). While most of the radiation emitted from DU is in the form of alpha particles, beta particles and photons may be released as decay products (WHO, 2001).

DU is produced in large quantities in the process of enriching uranium and is used both for civilian and military purposes. The most frequent civilian uses of DU include aircraft materials, counterweights in some elevators, radiation shields in medical radiation therapy machines, and containers for the transportation of radioactive materials. Military applications include the use in armor piercing munitions and armor plate for military vehicles such as tanks (ATSDR, 2003).

In military settings, the major risk is the DU dust generated when DU ammunition hits hard targets. There is also concern about contamination from shrapnel wounds and damage to the kidneys. Gulf War veterans with DU retained shrapnel fragments had

persistently elevated urinary uranium excretion more than 10 years after initial exposure (McDiarmid et al., 2004).

In occupational settings, most of the DU exposures are the result of inhalation. Depending on the amount of DU particulate matter, inhalation may lead to a protracted exposure of the lung and other organs (Bleise et al., 2003). A review of 11 studies in uranium miners attributed an increase risk of lung cancer to radon and its progeny and not to uranium (McDiarmid, 2001; Kathren and Moore, 1986; Kathren et al., 1989).

At IAAAP, safety reports indicate that several pounds of uranium-238 were routinely converted to a fine oxide powder during each hydrodynamic explosive (hydroshot) test performed at Firing Site 12 (Fuortes, 2001). It is estimated that 8,800 pounds of depleted uranium were exploded in 701 hydroshots between 1965 and 1973. Firing site employees were responsible for picking up the hot shards of depleted uranium after the explosion. A 1969 Standard Operating Procedure describes protocols for burning normal or depleted uranium machine turnings intermixed with explosive or mock explosives. Burn pad ash residue containing excessive alpha radiation contamination was collected in plastic bags and shipped to Pantex for burial (Fuortes, 2001).

Organic Solvents

Exposure of organic solvents in the workplace is common and constitutes an important occupational hazard. Organic solvents are a chemically diverse group of liquids or gases characterized by their ability to dissolve oils, fats, resins, rubber and plastics. During recent decades, the exposure levels have decreased due to increased education and safety measures. The list of industrial chemicals is long and many of the commercial products consist of combinations of several solvents. For example, Stoddard solvent and thinner (hydrocarbon mixtures) are components of many products, including paints, varnishes, adhesives, glues, coatings, degreasing and cleaning agents, dyes and printing inks, floor and shoe polishes, waxes, agricultural products and fuels (White and

Proctor, 1997). Common agents include n-hexane, methyl-n-butyl ketone, benzene, toluene, styrene, methylene chloride, carbon tetrachloride, chloroform, trichloroethylene, perchloroethylene, methanol, ethylene glycol, carbon disulfide, dimethylformamide, tetrahydrofuran, and ethylene oxide. All types of organic solvents are volatile liquids at room temperature and are lipophilic. The two main routes of exposure are through inhalation and skin contact (White and Proctor, 1997). Exposure dosage depends on several factors, including route of exposure, air concentration of the solvent, the solubility of the solvent in blood and the respiration rate of the exposed person (White and Proctor, 1997). Most solvents cause mucous membrane and skin irritation, for example eczema on the hands of workers. Other effects are more subtle and harder to diagnose, such as central nervous system symptoms. Short-term high-level exposures may produce narcotic effects. The narcotic effect of a solvent is directly related to its solubility in fat, and associated bioavailability in lipid-rich cerebral tissues (Mikkelsen et al., 1988). Acute symptoms may be reversible and include headache, dizziness, confusion, a feeling of inebriation, and unconsciousness (Rosenstock et al., 2005). Death may occur with some acute exposures.

Central nervous system symptoms of chronic organic solvent exposures are often insidious and diagnosed through neurobehavioral and psychometric testing. Solvent-exposed workers commonly describe frequent headaches, memory problems, concentration difficulties, affective changes (such as aggressiveness, irritability and depression), fatigue, dizziness, decreased libido, insomnia, and hyperautonomic symptoms (such as palpitations and increased sweating) (Rosenstock et al., 2005).

Certain cancers have been associated with chronic solvents as well. Heavy benzene exposures are known to induce pancytopenia, leukemias and lymphomas. Exposure-response calculations have suggested that benzene may pose a significant cancer risk at low exposure levels. In a cohort of workers chronically exposed to benzene in rubber hydrochloride plants, stratification according to levels of cumulative exposure

was performed. The standardized mortality ratios for leukemia increased from 109 to 322, 1186, and 6637 with increases in cumulative benzene exposure from less than 40 parts per million-years (ppm-years), to 40 to 199, 200 to 399, and 400 or more, respectively (Rinsky et al., 1987). Follow-up of these workers until 1996 continued to show significant relative risks with cumulative exposure but the risk diminished with time (Rinsky et al., 2002).

Trichloroethylene (TCE) exposure has been associated with neuropsychiatric symptoms, trigeminal neuralgia, hepatic toxicity, and multiple cancers. TCE is used as a degreasing agent primarily in the iron/steel and the laundry/dry cleaning industries. Evidence of excess cancer incidence among occupational cohorts with the most rigorous exposure assessment is found for renal cell carcinoma (RR = 1.7, 95% CI 1.1-2.7), liver cancer (RR = 1.9, 95% CI 1.0-3.4), and non-Hodgkin lymphoma (RR = 1.5, 95% CI 0.9-2.3) as well as for cervical cancer, Hodgkin lymphoma, and multiple myeloma (Wartenberg at al., 2000). However, since few studies isolate trichloroethylene exposure, results are likely confounded by exposure to other solvents and other risk factors (smoking and alcohol use). Results of a German hospital-based case –control study of metal-working workers who used TCE exclusively for degreasing purposes showed an elevated risk of renal cell carcinoma (OR 10.8, 95% CI 3.4-34.34.8 with 19 exposed cases) (Vamvackas et al., 1998).

Other carcinogenic solvents include ethylene oxide, commonly used in gas form, which irritates the respiratory tract and the skin at very low concentrations. It has been used for sterilizing hospital equipment and food. A cohort study of 18,235 workers handling ethylene oxide workers demonstrated an increase risk of death from bone cancer, although there were only 6 cases (Steenland et al., 2004). A study of workers that manufactured the solvent in Sweden demonstrated increased risk of death from cancer and diseases of the circulatory system (Hogstedt et al., 1979).

High Explosives (TNT, DNT, RDX, HMX and Tetryl)

Many AEC/DOE workers at IAAAP were routinely exposed to various high explosives through process of formulation, melting, pouring, packing and extensive machining to manufacture shaped charges (Fuortes, 2001). Several former workers described extensive dermal and hair discoloration resulting from exposure to high explosives.

2, 4, 6 Trinitrotoluene (TNT) is an organic nitrogen compound used in high explosives manufacturing. Concern about the toxicity of TNT dates to World War I when munitions workers exposed to TNT developed severe clinical hepatitis and aplastic anemia (Hathaway, 1977). Similarly, male workers from an ordnance factory in the United Kingdom were evaluated for hematologic abnormalities after reporting exposures from TNT and other industrial chemicals. Several industrial chemicals had elevated odds ratio for hematologic disorders, including TNT (OR =2.4) (West and Stafford, 1997). In the U.S., liver disease has been demonstrated in munition workers who were exposed to TNT over a period of 20 years (Goodwin, 1972). An elevated rate of lymphohematopoietic cancers has been associated with TNT as well. A clinic-based case-control study of occupational risk factors among 100 patients diagnosed with leukemia compared with 100 controls revealed an association with nitro-organic explosives (Nisse et al., 1995).

Other organic nitrogen compounds, 2,4 and 2,6-dinitrotoluene (DNT) are intermediates in the manufacture of TNT. They are also used in the polymer industry, mostly in the production of polyurethane foams. The primary targets of DNT toxicity are the hematopoietic system (pallor, cyanosis, anemia, and leukocytosis), the cardiovascular system (ischemic heart disease), the central and peripheral nervous systems (weakness, headache, dizziness, nausea, insomnia, and neuropathy) and the reproductive system (reduction of sperm counts, alteration of sperm morphology, and aspermatogenesis) (Tchounwou et.al, 2003). Some occupational studies have not shown increased mortality

from cardiovascular disease in workers exposed to DNT, but studies are limited by healthy worker effect and small sample size (Stayner et al., 1992).

There have also been positive associations with malignancy. A total of 4,989 workers exposed to DNT and 7,436 unexposed workers who had worked for at least 5 months at munitions factories between 1949 and 1980, were studied. Workers were considered exposed if they had worked at least 1 day on a job with probable exposure to DNT. An excess of hepatobiliary cancer was observed among workers exposed to DNT in this study. The rate ratio for hepatobiliary cancer was 2.67 (six cases observed) based upon comparison with the US population (SMR = 2.67, 95% CI = 0.98-5.83), and 3.88 based upon comparison using the internal unexposed referent group (SRR = 3.88, 95% CI = 1.04-14.41) (Stayner et al., 1993). This study failed to demonstrate an exposure-response relationship between duration of DNT exposure and hepatobiliary cancer mortality, although the sample size of workers with long duration of exposure to DNT was very small.

Other high explosives include Hexahydro-1, 3, 5-trinitro-1, 3, 5-triazine (RDX or Cyclonite) and Octahydro-1, 3, 5, 7 teranitro-1, 3, 5, 7- tertazocine (HMX). Both may cause neurologic symptoms and hepatotoxicity after exposure. Other than case-reports, few human studies have closely evaluated the chronic effects of exposure.

IAAAP workers exposed to Tetranitromethylaniline (Tetryl) describe yellowing of skin and hair (sweating their sheets and clothes to a yellow color) and dermatitis (Fuortes, 2001). Other effects include gastrointestinal symptoms, central nervous system effects, chronic hepatitis and delayed hypersensitivity reactions (Fuortes, 2001).

Beryllium

Beryllium is a naturally occurring, silver-grey metal. Lighter than aluminum and more rigid than steel, beryllium has many unusual properties which make it ideal for several applications, including aircraft and space vehicle structure, x-ray machine

assemblage, mirrors, ceramics, metal alloys, and, since the 1950's, nuclear technology including weapons and reactors (ATSDR, 2003). Metallic beryllium has good resistance to alteration or chemical attack and is not easily altered to soluble forms when released to the environment (ATSDR, 2003). At IAAAP, worker reports indicated on-site use of beryllium alloy chisels/scrapers, honing (sanding and grinding) the non-sparking beryllium tools and working with beryllium plates that crushed explosives (Fuortes, 2001).

Beryllium was used as the neutron reflector material ('pit liner') in most American nuclear weapons and in contemporary thermonuclear 'primaries'. The 'primary', or weapon trigger, consists of three components: the central spherical plutonium 'pit' or core, the Beryllium 'pit liner', and a surrounding high-explosives shaped-charge (ATSDR, 2003).

The most significant disadvantage of beryllium as an industrial material appears to be the toxicity of its dust, fumes, and soluble salts. Wipe or vacuum samples conducted from 1970-1974 at various work areas within Line 1 showed elevated concentrations of beryllium dust (Fuortes, 2001). The concentrations reported ranged from non-detectable to 1,000 mg beryllium per sample with no reference to surface area in a 1971 report; non-detectable to 4 mg/100 cm2 in a 1973 report; and non-detectable to 112 mg/100 cm2 in a 1974 report (Fuortes, 2001 and Mikulski et al., 2010). A recent 2007 survey of surface contamination was performed in an area where millwrights had occasionally used belt sanders to resurface alloy tools. Results revealed only two samples out of one hundred collected throughout the facility which exceeded the DOE surface contamination housekeeping level of 3.0 mg/100 cm2 (Sanderson et al., 2008).

Beryllium is carcinogenic in animal studies. In humans, two types of lung disease can result from the inhalation of beryllium fumes, dust or both. Acute lung injury can occur from short-term, high intensity exposure and chronic granulomatous disease can result after low exposures over months to years (Infante and Newman, 2004). Evidence

suggests that chronic beryllium lung disease can have a long latency period and is not clearly related to duration of exposure (Fuortes, 2001). Beryllium sensitization and chronic beryllium disease cases have been previously reported for employees at the Rocky Flats Environmental Technology Site (Stange et al., 1996 and 2001). Rocky Flats is part of the U.S. Department of Energy weapons complex which began using beryllium in research and development operations in 1953. The Rocky Flats Beryllium Health Surveillance Program, initiated in June 1991, was designed to provide medical surveillance for employees exposed to beryllium (Stange et al, 1996). The prevalence of beryllium sensitization and chronic beryllium disease by job category was examined among individuals tested in the surveillance program. Beryllium machinists (OR 3.04, 95% CI 1.48-3.97), health physics technicians (OR 2.87, 95% CI 1.12-7.36) and custodial employees (OR 1.30, 95% CI 0.92-1.85) had an increased prevalence of beryllium sensitization (Stange et al., 2001). Finally, increased mortality due to lung cancer was observed among 9,225 male workers employed at U.S. beryllium processing facilities (Ward et al., 1992).

Asbestos

Asbestos is the name given to a group of six different fibrous minerals (amosite, chrysotile, crocidolite, and the fibrous varieties of tremolite, actinolite, and anthophyllite) that occur naturally in the environment (ATSDR, 2008). Asbestos minerals have separable long fibers that are strong and flexible enough to be spun and woven and are heat resistant (ATSDR, 2008). The fibers are microscopic and may become aerosolized during manufacturing processes where they are easily inhaled. Inhalation represents the major route of exposure. Fibers are inhaled deep into the respiratory tract causing a chronic inflammatory response. Physical signs include pleural plaques (Sison et al., 1989), pleural thickening (Kee et al., 1996), exudative pleuritis (Hillerdal and Ozesmi, 1987), and atelectasis (Hillerdal, 1989). The presence of pleural plaques indicates

significant exposure to asbestos and is associated with a ten-fold increased risk for development of mesothelioma (Hillerdahl, 1994). Specific trades considered at high risk for asbestos exposure include insulators, sheet-metal workers, plumbers and pipefitters, steamfitters, boilermakers, plasterboard workers and numerous shipyard trades such as electrician and shipscalers (Rosenstock, et al., 2005 and Barnhart et al., 1997). Asbestos insulators and other jobs with the highest asbestos exposures have shown that workers have a shorter life-expectancy due to lung cancer, mesothelioma and asbestosis (Berry, 1981). Need assessment surveys performed at former DOE sites have listed asbestos as one of the main exposures and have recommended that workers receive screening exams for pulmonary disease (Breysse et al., 2002).

<center>Background Studies of Atomic Weapons Workers</center>

Current radiation standards are derived primarily from studies of survivor groups exposed to large doses of radiation over a short time period. Risk assessments for radiation protection in the workplace have to rely on epidemiologic data from these cohorts in order to understand the potential health effects a worker may experience from radiation exposure. Historically, the primary groups studied have been the survivors of the Hiroshima and Nagasaki atomic bombings. The current recommendations for protection against low-LET radiation in the workplace are a result of studies conducted on a cohort of the atomic bomb survivors, a population exposed primarily to high-doses in a short time frame. Mortality studies from 1950 to 1990 on this cohort have documented excess deaths from solid cancers and most leukemias (Pierce, 1996). Marked increases in breast cancer cases were seen in women exposed to 10 rads or more with latency more than 10 years from exposure (McGregor et al., 1977 and Land, 1995). Similarly, the 1986 Chernobyl accident resulted in high cumulative doses in certain subpopulations that may have equaled or exceeded the Hiroshima/Nagasaki bombings (Burkhart, 1996). An increase in thyroid cancer has been clearly demonstrated in

children exposed to radioactive iodine (principally ^{131}I) released during the reactor accident (UNSCEAR, 2000).

While these studies are relevant to populations exposed to high-dose rate acute exposures, the use of these data to estimate the effects of low-dose chronic exposures is inexact. Models have been developed to extrapolate the risks from high doses to low doses and from acute exposures to chronic exposures but are subject to uncertainty (Cardis et al., 1995). Current radiologic protection standards were estimated from the high-dose studies which recommends no more than 5 rem/year. The continued study of the health effects of chronic low-dose radiation is relevant to the growing body of research in occupational epidemiology.

Early studies of workers exposed to high dose radiation were among the first to demonstrate the carcinogenic effects of radiation. Women working as radium dial painters were shown to have an increased incidence of breast cancer (Adams, 1980 and Stebbings, 1984). Other examples include: carcinomas of the skin in radiologists and x-ray workers, leukemias in early radiologists, lung cancers in pitchblende and other underground hard-rock miners, and osteogenic sarcomas and carcinomas of the cranial sinuses in early radium watch dial painters (Rosenstock et al., 2005).

In addition to the studies described above, studies on workers of nuclear weapons facilities provide data to estimate radiation induced cancer mortality and cancer incidence. The Mayak facility located between the cities of Chelyabinsk and Ekaterinburg in the Russian Federation included a nuclear reactor and a radiochemical processing plant for plutonium extraction from exposed fuel (Koshurnikova et al., 1994). Nuclear workers from the former Soviet Union were exposed to both external and/or internal radiation at doses much higher than standards acceptable today. A registry of approximately 18,830 workers employed at different times has been collected. Weapons production started in 1947 and adverse radiation conditions prevailed at both facilities during the early years of operation. Numerous accidents occurred at the plant resulting in

large, mostly external gamma-radiation exposures to the workers (Koshurnikova et al., 1994). Many of the workers were also exposed to inhaled plutonium at levels much higher than permissible today. Previous studies of the Mayak nuclear weapons facility have shown a significant increase in the total cancer mortality rate (Koshurnikova et al., 1994 and 1996). When compared to population rates of malignancies in the Soviet Union, an increase in malignancies of the hematologic and lymphatic systems were noted in a cohort of men working in the radiochemical processing plant in the early years of production (Koshurnikova et al., 1994). Results of analyses of plutonium-related lung cancers have been reported (Khokhriakov et al., 1994 and 1998, Tokarskaya et al., 1995 and 1997, Koshurnikova et al., 1998 and Kreisheimer et al., 2000). An increase in lung cancer incidence from high levels of radiation exposure were demonstrated when exposures were calculated using total occupationally accumulated radiation (external plus internal incorporation of plutonium) (Hohryakov et al., 1994). A case-control study of Mayak workers that accounted for smoking, other occupational lung disease, external gamma radiation and airborne [239]PU between the years 1949-1957 found an increase in adenocarcinoma of the lung in workers with high internal [239]PU exposures (OR 2.9, 95% CI =1.0-8.4) (Tokarskaya et al., 1995 and 1997). Liver and bone cancer mortality risks were also higher for Mayak workers who were exposed to both internal and external radiation (Gilbert et al., 2000 and Koshurnikova et al., 2000). Continued study of the Mayak workers will provide valuable information on the effects of plutonium exposure and of exposure protraction in the high-dose range.

Nuclear industry workers in the United States and United Kingdom may represent relevant populations to study the effects of low dose chronic exposures to external radiation. While the exposures to the Mayak workers are relevant to comparisons to early AEC\DOE workers in the United States, concerns remain that these exposures are not representative of the lower dose exposures received by the U.S. workers over an extended period of time. About fourteen current and former AEC/DOE facilities have

been studied previously (Alvarez, 2000). Findings from these cohorts have been mixed, but have suggested an increased mortality for a number of cancer and non-cancer outcomes. Table 1.6 displays a summary of statistically significant all cause and all cancer mortality findings from the AEC/DOE facilities. Table 1.7 displays the statistically significant elevated cause-specific mortality findings from each AEC/DOE site as well.

Below is a detailed review of the studies conducted at the individual AEC\DOE facilities. Radiation units are reported in the units (i.e., International units or special units) to maintain consistency with the original article (Table 1.2 reviews equivalent units of radiation dose).

Oak Ridge National Laboratory X-10 Site, Tennessee

There are three major DOE sites in the Oak Ridge area: the Oak Ridge National Laboratory (ORNL) X-10 reactor site, the K-25 gaseous diffusion plant, and the Y-12 site (formally the site of the electromagnetic separator). While multiple studies have been conducted with data from ORNL, most have focused on the X-10 reactor site where workers were individually monitored for whole body exposure to ionizing radiation for the period 1943-1985. Initially, radiation was measured using pocket ionization chambers from 1943-1944, film badges (or security badge) dosimeters were used from 1944-1975, and thermoluminescent dosimeters were used from 1976 (Wing et al., 1994). The first retrospective cohort mortality studies conducted among 8,375 white males with follow-up through 1977 found no associations between external penetrating radiation and mortality from all cancers (Checkoway et al., 1985 and Gilbert et al., 1989b). The radiation doses were primarily from gamma rays and were generally low; the median cumulative exposure for a worker was 0.16 rem (Checkoway et al., 1985). In follow-up studies through 1984, positive associations were reported in a number of studies (Wing et al., 1991 and 1993, Gilbert et al., 1993b, Frome et al., 1997). In a cohort consisting of

8,318 white males with exposure data gathered from film badges, relative low mortality was found when compared to the general population of white men in the United States (Wing et al., 1991). Leukemia mortality was elevated in the total cohort and in workers who had at some time been monitored for internal radionuclide contamination (Wing et al., 1991). After accounting for age, birth cohort, socioeconomic status, and active workers status, external radiation with a 20-year exposure lag was related to all causes of death (2.68% increase per 10 mSv) primarily due to cancer mortality (4.94% per 10 mSv) (Wing et al., 1991). This study was met with considerable skepticism due to the finding of an unexpectedly large relationship between low-level external penetrating ionizing radiation and deaths from cancer. The authors found that the risk of dying is ten times greater than extrapolations from high dose studies of Japanese atomic bomb survivors (Wing et al., 1991). In response, adjustment for date of hire, employment duration, exposure to beryllium, lead and mercury had little effect on radiation risk estimates (Wing et al., 1993).

In a follow-up mortality study through 1990, a cohort of 14,095 workers comprising of men, women and nonwhites were studied (Richardson and Wing, 1999). Positive associations were observed between low-level exposure to external ionizing radiation and mortality, especially for doses received after 45 years of age (Richardson and Wing, 1999). Associations were larger under longer latency periods and primarily due to cancer associated deaths.

Oak Ridge Y-12 Plant, Tennessee

The Oak Ridge Y-12 Plant produced nuclear materials starting in 1943, and the mortality statistics of the workers were examined from 1947 through 1974. As a uranium processing facility, workers were exposed to various compounds of uranium 235 and uranium 238. Workers were also exposed to other agents including solvents, machine oils, mercury, lead and beryllium (Loomis, 1996). An initial study of 6,781 white males

found an excess mortality from lung cancer that was quantitatively related to internal alpha and external gamma radiation dose (SMR 1.4, 95% CI 1.1-1.7) (Checkoway et al., 1988). Mortality from brain cancer and lymphopoietic system cancers was also elevated, SMR of 1.8 and 1.9 respectively, but based on a small number of deaths (Checkoway et al., 1988).

In a follow-up mortality study as in 1990, the worker population consisted of 8,116 men and women with 1,861 deaths and 206 lost to follow-up. Death rates from brain cancer and several lymphopoietic system cancers were also elevated among white males with SMRs of 1.28 and 1.46 respectively (Loomis and Wolf, 1996). A 20% excess of lung cancer was seen in 6,591 of the white males (SMR 1.20, 95% CI 1.04-1.38) and an excess of breast cancer among the 1,073 female workers (SMR 1.21, 95% CI 0.60-2.17) (Loomis and Wolf, 1996). Mortality from cancer of the pancreas, prostate and kidney was only slightly elevated. Similar to Oak Ridge National Laboratory, total mortality was low for all the Y-12 workers indicative of a healthy worker effect (Checkoway et al., 1988 and Loomis and Wolf, 1996).

K-25 Gaseous Diffusion Plant, Tennessee

The study population consisted of 37,712 ever employed workers (30 days or more), which included males, females and all races employed at the Oak Ridge K-25 Gaseous Diffusion Plant from 1945 to 1984. Workers were potentially exposed to external penetrating radiation, internal alpha radiation, epoxy resins, metallic nickel, uranium hexafluoride, insoluble uranium oxides, hydrofluoric acid, solvents, and fluorocarbons (Dupree et al., 1994). Unlike most of the DOE studies, no healthy worker effect was observed in the K-25 workers. For white males, the SMR for all causes of death was significantly elevated (SMR 1.03, 95% CI 1.01-1.05). Other statistically significant increases among the white male population included cancers of the respiratory system including lung cancer (SMR 1.19), cancer of the bone (SMR 1.82), mental

disorders (SMR 1.82), and all respiratory diseases (SMR 1.19), including pneumonia (SMR 1.17) (Dupree et al., 1994). Among nonwhite males, no cause of death showed a statistically significant increase.

<center>Hanford nuclear materials production site, Washington</center>

The Hanford operations were larger than those at ORNL. Increased risks of dying from all cancers were reported with a positive correlation related to occupational doses in two studies (Mancuso et al., 1977 and Stewart and Kneale, 1996). There were 3,520 certifiable deaths documented among 35,000 white males who were employed between 1943 and 1972. Exposure from internal penetrating radiation was assessed from urine-monitored workers. Workers who had died from cancer were found to have had a higher average dose of low-level radiation than workers who had died from other causes (Mancuso et al., 1977). The difference was largely the result of radiation received after 40 years of age and more than 10 years before death (Mancuso et al., 1977). A recent follow-up study evaluating the influence of age at exposure on radiation risk estimates showed the excess relative risk per sievert (ERR/Sv) for cumulative radiation dose accrued at ages 55 and above (with a 10-year lag) was 3.24 (90% CI:0.80 to 6.17) (Wing, 2005). This association was primarily due to an association with lung cancer (ERR/Sv 9.05, 90% CI 2.96 to 17.92) (Wing, 2005).

Mortality studies of Hanford workers were conducted in 1981, 1986 and 1989 (Gilbert et al., 1989a, Gilbert et al., 1993a, Stewart and Kneale, 1996). There was little evidence of a positive correlation of cumulative occupational radiation dose and mortality from leukemia and from all cancers (excluding leukemia) (Gilbert et al., 1993a). Mortality from cancer of the pancreas (p=0.07), multiple myeloma (p=0.05) and Hodgkin lymphoma (p=0.04) showed positive correlations with radiation dose that approached statistical significance (Gilbert et al., 1993a). In a nested case-control study that used follow-up data to 1989, there was evidence of a dose-related risk due to radiation

exposure received at least 15 years before a cancer death and during the last 10 years of working life (between 55 and 65 years of age) (Stewart and Kneale, 1996). However, the relative frequency of site-specific cancers showed no signs of being different for radiogenic and idiopathic cancers and no association between radiation at the highest exposure level and leukemia (Stewart and Kneale, 1996).

A methodological study compared all causes of death for 35,000 white male Hanford workers to all causes of disability filed through the Social Security Administration (Mancuso, 1993). In general, a high percentage of the causes of disability were not recorded by death certificate for ICD categories of disease or specific cancer sites and may represent an underestimation of the true magnitude of occupation health effects (Stewart and Kneale, 1996).

Finally, the healthy survivor effect (HSE) was studied among male and female Hanford workers (Baillargeon et al., 1999). HSE is a type of survivor bias in which healthy workers stay and continue working in the workforce while unhealthy workers leave. Follow-up mortality data on 44,154 employees from the Hanford nuclear facility for the period of 1944–1986 were used to estimate the HSE. Results demonstrated a survival advantage for some subgroups in the longest employment stratum but not for others. Among Hanford males, all of the subgroups under study demonstrated a survival advantage in the 30+ year stratum except those hired at or after age 40 (Baillargeon et al., 1999). Females under 40 years old at hire did not demonstrate a HSE, however, those hired after 40 years old and employed for at least 30 years experienced longer survival (Baillargeon et al., 1999).

Fernald Feed Materials Production Center, Ohio

In 1952, employees who were potentially exposed to high levels of external radiation were monitored weekly and those exposed to lower levels were monitored biweekly (Cragle et al., 1995). By the mid-1950s all workers were monitored monthly,

and non-routine internal exposure monitoring (by urinalysis) was also performed. Subsequent exposures assessments were calculated for both internal and external radiation. Fernald workers were exposed to insoluble uranium compounds and multiple chemicals such as nitric acid, sodium hydroxide, tributyl phosphate, trichloroethylene and kerosene. Mortality patterns were examined for 4,014 white males between 1951 and 1981, with 1,064 deaths among this population. Although salaried workers showed a healthy worker effect, significant increases for deaths from stomach cancer (SMR 2.61, 90% CI) were found in this subcohort (Cragle et al., 1995). Separate analysis performed on hourly workers did not demonstrate a healthy worker effect but did exhibit an excess mortality from all cancers (SMR 1.21), lung cancer (SMR 1.26), and motor vehicle injuries (SMR 1.27) (Cragle et al., 1995). For all workers, chronic non-malignant respiratory disease showed a positive dose-response relationship with internal radiation exposure. Dose-response analyses for lung cancer with external radiation dose revealed an excess relative risk of 8.0/Sv with a 10-year lag and 10.7/Sv with a 15-year lag (Cragle et al., 1995).

In a separate study, cancer mortality among Fernald workers exposed to chemicals during uranium processing was examined. The uranium work conducted at the Fernald facilities involved the processing of uranium-ore concentrate and uranium of low-enrichment grade into fabricated uranium metal products, including thorium metal. Workers used large amounts of nonradioactive industrial chemicals, many of which are potent respiratory irritants) hydrofluoric acid, ammonia, nitric and sulfuric acid, tributyl phosphate) or suspected carcinogens (trichloroethylene and cutting fluids) (Ritz, 1999). The cohort consisted of 3,814 white male employees hired for at least three months between 1951 and 1972. Analyses focused on exposures to trichloroethylene, cutting fluids and kerosene, while controlling for internal and external radiation exposures. Results demonstrated that exposure to heavy concentrations of trichloroethylene was strongly associated with liver cancer (RR 12.1, 95% CI 1.03 to 144) (Ritz, 1999). In

addition, workers exposed to moderate and heavy amounts of cutting fluids had an excess number of rare cancers of the larynx (exposure duration > 5years, RR 236, 95% CI 9.93 to 5630) (Ritz, 1999). Overall, the mortality rate of the Fernald workers was lower than that for U.S. white males, suggesting a strong healthy worker effect.

<div align="center">Mallinckrodt Chemical Works, Missouri</div>

Mallinckrodt Chemical Works processed tonnage quantities of uranium ore into pure uranium tetrafluoride and metal between 1943 and 1966. For about 10 years within this time period, high-grade uranium ore from the Belgian Congo was processed using crude standards. Some workers were exposed to high levels on both internal and external radiation (Dupree-Ellis et al., 2000). A retrospective cohort mortality study of white male workers was conducted using external radiation doses estimated from film badges that monitored β- and γ-radiation exposure. Of the 20.8% of workers that did not have monitoring results available, doses were estimated using an algorithm (Watkins et al., 1997). The SMR was 0.90 for all causes of death and 1.05 for all cancers (Dupree-Ellis et al., 2000). Among the cancer sites that had at least 30% elevated excess over expected mortality were esophagus (SMR 1.35, 95% CI 0.61-2.62), rectum (SMR 1.48, 95% CI 0.71-2.67), brain (SMR 1.57, 95% CI 0.84 to 2.64) and multiple myeloma (SMR 1.30, 95% CI 0.42 to 3.03) (Dupree-Ellis et al., 2000). A dose-response relationship was indicated between external radiation and kidney cancer (10 cases) with an excess relative risk estimate of 10.5/Sv (the mean cumulative dose was 47.8 mSv) (Dupree-Ellis et al., 2000). This finding may be due to chance or to other exposures such as internal radiation and/or silica (Dupree-Ellis 2000). Similarly, the SMR for chronic nephritis was 1.88 (6 cases) which could further indicate an exposure from another substance. Kidney cancer hasn't been associated as a radiogenic cancer site in atomic bomb survivor studies (Pierce et al., 1996) and only one other study of uranium processing plants has shown a similar dose-response relationship (Fraser et al., 1993).

Savannah River Site, South Carolina

The Savannah River Site is located near Aiken, South Carolina and was constructed to produce nuclear weapons in 1950. Operations included uranium processing, nuclear fuel fabrication, nuclear reactor operation, nuclear reactor refueling, nuclear fuel reprocessing, and thorium processing (between 1965 and 1972) (Cragle et al., 1988). A retrospective cohort mortality study was conducted in a population of 9,860 white male workers using personnel data from 1952 to 1981. From 1951 to 1957 film badges were processed on a weekly basis, processed bi-weekly from 1958 to 1964 and then monthly from 1965. Internal radiation exposures were assessed through random urinalysis and whole body counts. Because the Savannah River Site was managed by one contractor, the DuPont Corporation from 1952 to 1987, it is considered to have some of the best dosimetric data on its employees (Cragle et al., 1988). For this study, data for hourly and salaried employees were analyzed separately by time period of first employment and length of employment. There was a strong healthy worker effect when results were compared with mortality rates in the U.S. population. Radiation monitoring data were assessed only for the leukemia deaths. The mean cumulative radiation dose equivalent (external whole body dose plus internal effective dose) was 4,675 mRem with a median of 920 mRem (Cragle et al., 1988). Results demonstrated a statistically significant increase in leukemia mortality (6 observed vs. 2 expected, SMR 2.75) in a sub-set of hourly employees hired before 1955 (employed 5-15 years) (Cragle et al., 1988). None of the workers who died of leukemia received reported radiation exposures above 5 rem, which is the current annual occupation radiation limit.

A recent updated study evaluated the mortality experience of 18,883 Savannah River Site workers hired between 1950 and 1986 showed employees have fewer deaths due to all causes and all cancers than expected based upon U.S. and South Carolina referent rates (Richardson et al., 2007). Workers were potentially exposed to a range of chemical and physical hazards, ionizing radiation and asbestos. The SMR for cancer of

the pleura for men was significantly elevated (SMR 4.25, 90% CI 1.99 to 7.97). Monthly-paid and hourly-paid workers also had a non-significant increased risk of leukemia (SMR 1.33, 90% CI 0.88 to 1.93) and (SMR 1.36, 90% CI 1.02 to 1.78) respectively (Richardson et al., 2007).

A separate study on Savannah workers was performed analyzing leukemia mortality on 18,883 employees who were monitored for both internal and external radiation. The exposures of interest were defined as cumulative whole-body radiation dose equivalent in millisieverts from external sources (dosimeters) and internal tritium depositions via bioassay monitoring. A positive association was observed between leukemia (all types combined) mortality and radiation dose under a 3-year lag assumption (ERR/10 mSv = 0.04, 90% CI 0-0.12) (Richardson and Wing, 2007). The association was of larger magnitude for leukemia (excluding chronic lymphocytic leukemia) and myeloid leukemia.

<div align="center">Linde Air Products Company, New York</div>

A small retrospective cohort mortality study on 995 men employed more than 30 days by Linde Ceramics Plant between 1943 and 1949. Employees were exposed to uranium (ore with a high radium-226 content, tetrafluoride, uranium oxide, uranium trioxide and uranium dioxide) and other exposures such as, nickel powder, chlorine, hydrofluoric acid, lead, sulfate nitric acid, nitrogen oxides, silicon dioxides and sulfuric acid (Dupree et al., 1987). Internal radiation exposure was estimated by study of plant operational reports, monitoring data, and personal commentary from contemporary employees. Elevated SMR values were observed for all causes of death when compared to the U.S population (SMR 1.18, 95% CI 1.07-1.30). Other statistically significant increases were observed for laryngeal cancer (SMR 4.47, 95% CI 1.44-10.43), all circulatory diseases (SMR 1.18, 95% CI 104-1.35), arteriosclerotic heart disease (SMR 1.19, 95% CI 1.01-1.39), all respiratory diseases (SMR 1.52, 95% CI 1.04-2.14),

including pneumonia (SMR 2.17, 95% CI 1.26-3.47) (Dupree et al., 1987). The elevated all-cause death rate above that of the U.S. population and lack of excess lung cancer are unique findings and contrary to previous findings of uranium workers. No significant association was found with length of employment or work in the most hazardous areas of the plant.

<div align="center">Mound Laboratory, Ohio</div>

This study focused primarily on exposure to polonium-210 (^{210}Po), a naturally occurring decay product of uranium. Workers were mainly exposed by inhalation of the soluble form of Po during the separation and chemical preparation of Po (Wiggs et al., 1991). The cohort consisted of 4402 white males employed at the Mound facility from 1944 to 1972. About 49.5% of the men were monitored for Po uptake by means of urine bioassays. Results indicated no excess mortality when compared to the general population. More lung cancers were observed than expected (46 vs. 40.2) based on U.S. rates, but the SMR for lung cancer was not significantly elevated (SMR 1.13, 90% CI 0.87-1.44) (Wiggs et al., 1991). Dose-response trends were also negative. Similarly, when compared to Ohio rates, the SMR for lung cancer was non-significant at 1.06.

A mortality study investigated the effects of external ionizing radiation using monitoring data from a subcohort of 3,229 workers (Wiggs et al., 1991a). The original cohort consisted of 4,182 white males employed at the Mound facility between 1947 and 1979. No statistically significant elevations for mortality or site-specific cancers were detected. Dose-response analyses conducted on the subcohort of men exposed to external radiation revealed a statistically significant (p<0.01) dose-response trend for lymphopoietic/hematopoietic cancers and all leukemias (χ^2=9.48 and 12.05 respectively). In the 50mSv category, the standardized rate ratio (SRR) for all leukemia was increased (SRR 15.43, 95% CI 1.83-130.40) (Wiggs et al., 1991a).

Los Alamos National Laboratory (LANL), New Mexico

A small study of 26 (7 deceased by 1990) males who worked with plutonium (^{239}Pu) during World War II on the Manhattan Project at LANL was conducted (Hempelmann et al., 1973 and Voelz et al., 1979, 1985, 1991). The Manhattan Project designed and manufactured the first atomic bomb using plutonium in 1944-1945. The work was partly done in chemical fume hoods but some operations were performed in open rooms resulting in inhalation of Pu particles (Voelz and Lawrence, 1991). Participants were selected based on individual job assignments, work conditions, and the results of Pu measurements in urine samples taken during that time period. The Pu-exposed workers had medical examinations about every 5 years, over a period of 42 years, until 1987. Individual Pu depositions, including lung burdens, as of 1987 or time of death, ranged from 52 to 3180 Bq (1.4 to 86 nCi) with a median value of 500 Bq (13.5 nCi) (Voelz and Lawrence, 1991). The overall mortality experienced by the workers was below that expected from U.S. population rates; however, the results were not statistically significant due to the small sample size. Comparisons were also made with 876 unexposed, contemporary Los Alamos workers and also concluded that the mortality experience of the 26 highly exposed workers was not excessive. Three of the men died from lung cancer and one from osteosarcoma. All three of the men who died from lung cancer had smoking histories so it was impossible to determine how much additional risk may have been imposed by Pu exposure (Voelz and Lawrence, 1991).

In another mortality study through 1990; a cohort of 15,727 white men employed at LANL was evaluated using whole-body ionizing radiation and internal depositions of plutonium as the exposures of interest (Wiggs et al., 1994). The major forms of radiation exposure encountered by some of the workers are primarily from external radiation (x rays, gamma rays and neutrons) and internal exposures from tritium and plutonium isotopes. The results of the study indicated a low mortality in comparison with the general population. The authors attribute this to Healthy Worker Effect because the

population of workers were better educated, more affluent and may have smoked less. (Wiggs et al., 1994). A cross-sectional study of smoking prevalence conducted in the 1980s indicated that men employed by LANL at that time smoked at a much lower rate than the general U.S. population (Wiggs et al., 1994 and Mahoney et al., 1987). Analyses of mortality on a subcohort of 3,775 plutonium monitored employees, considering a 10-year induction period, were performed. Internal plutonium depositions were estimated from urine bioassays collected from potentially exposed employees from 1944-1984. The 303 "exposed" workers had a body burden estimated at ≥ 74 Bq. None of the resulting rate ratios for all causes and all cancers was significantly above 1.00.

For external ionizing radiation, monitored workers (by film badges and thermoluminescent dosimeters after 1980) were stratified into four dose categories: < 10, 10-49.9, 50-99.9, and 100+ mSv. A 10-year lag was considered for all cancers and all causes while a 2-year lag was considered for cancers of the lymphohematopoietic system. Statistically significant tests for trend were observed for three specific sites: Hodgkin lymphoma (trend test statistic 2.12, p=0.02), malignant neoplasms of the brain/CNS (trend test statistic 2.13, p=0.02), and cancer of the esophagus (trend test statistic 1.74, p=0.04) (Wiggs et al., 1994). Additional analyses were conducted to determine whether the dose-response analyses for external radiation were confounded by the dose from plutonium. When the workers with plutonium exposures were excluded, the dose-response trends for cancers of the kidney (trend test statistic 2.05, p=0.02) and lymphocytic leukemias (trend test statistic 1.73, p=0.04) were significant (Wiggs et al., 1994).

Zia Company, Los Alamos, New Mexico

A retrospective mortality study was conducted on 5,424 workers employed by Zia Company between 1946 and 1978. The workers were monitored for exposure to either plutonium or external ionizing radiation. The cohort included 365 females (354 whites

and 11 Native Americans) and 5,059 males (4954 whites, 94 Native Americans, 10 African Americans and 1 Asian). Of the men that were included as whites, about half were white Hispanic. Zia Company was the principal subcontractor to Los Alamos National Laboratory from 1946 to June of 1986. Workers mostly performed construction and maintenance functions at LANL. The sources of occupational radiation exposures for the Zia Company were external radiation, primarily gamma, and internal deposition of plutonium-238 and plutonium-239. Pocket chambers or film dosimeters were used for personnel monitoring from 1944 through 1980, when they were replaced with thermoluminescent dosimeters. Formal bioassay programs to monitor for internal exposures started in 1944. Among male workers, there were several significant SMRs: stomach cancers, senility and ill-defined conditions (injuries, motor vehicle collisions) (Galke et al., 1992). Hispanic male workers had significantly elevated SMRs for stomach cancers, all injuries and motor vehicle collisions (Galke et al., 1992). Non-Hispanic males had significantly elevated mortality from all causes, all cancers, lung cancer, all circulatory diseases and all respiratory diseases (Galke et al., 1992). Stratified rate ratio (RR) analyses were conducted to test the association between radiation exposure and mortality. No significant associations were seen in either Hispanic or non-Hispanic males in the plutonium or external ionizing radiation analyses.

A smaller mortality study of 224 male workers exposed to plutonium at LANL and Zia Company was performed. Participants were selected by searching the dosimetry records for all workers who were estimated to have plutonium depositions over 370 Bq. All the SMRs for malignant neoplasms were below 1.0, except for bone cancer (SMR 10.6, 95% CI 0.15-59), though this represented only one case (Voelz et al., 1993).

Incident cancers were ascertained from the New Mexico Tumor Registry for a group of LANL and Zia Company employees between 1969 and 1978 (Acquavella et al., 1983). Incident cancers were identified by a computer match of the Los Alamos employed roster against New Mexico Tumor Registry files. The resulting numbers of

total and site-specific cancers were compared to the numbers expected based on incidence rates for the State of New Mexico, specific for age, sex, ethnicity, and calendar period. For Caucasian males, significantly fewer cancers than expected (SIR = 0.60, 95% CI 0.44 to 0.79) were found (Acquavella et al., 1983). This resulted from marked deficits of smoking-related cancers, particularly lung (2 observed, 19.4 expected) and oral (1 observed, 6.5 expected) cancer. Similarly, no smoking-related cancers were detected among Caucasian females, though they had a slight non-significant excess of breast cancer (14 observed, 9.1 expected) and a suggestive excess of cancer of the uterine corpus (2 observed, 0.25 expected) (Acquavella et al., 1983). Investigators were not able to ascertain incident cancers among workers outside the state of New Mexico.

Rocky Flats Nuclear Weapons Plant, Colorado

A retrospective mortality study was conducted on 5,413 white males employed for at least two years by Rocky Flats Nuclear Weapons Plant from 1952 through 1979. The Rocky Flats Plant is located in Golden, CO and supplied nuclear components for the Pantex Plant in Texas. Risks from exposures to external radiation and low levels of plutonium were investigated. Smoking information was not available for this study. Internal plutonium exposures were estimated from urine bioassays and workers estimated to have 2 nCi (nanocurie) or more were defined as exposed. External radiation exposures were estimated using data from film badges and thermoluminescent dosimeter badges to create cumulative exposure. Workers with a cumulative exposure exceeding 1 rem were defined as exposed. Fewer deaths than expected were observed from all causes, all cancers, and lung cancer (Wilkinson et al., 1987). Excess deaths were noted for benign and unspecified neoplasms (SMR 3.76, 90% CI 1.77-7.07), which were later determined to be intracranial tumors after death certificates were reviewed. Several other cancers had high SMRs however, the confidence intervals were wide: liver/gallbladder (SMR 1.39, 90% CI 0.38-3.59), prostate (SMR 1.42, 90% CI 0.71-2.56), brain/central nervous

system (SMR 1.19, 90% CI 0.52-2.36), thyroid (SMR 3.70, 90% CI 1.9-17.57) (Wilkinson et al., 1987).

The second part of the study calculated rate ratios for employees with plutonium depositions of 2 or more nCi compared with those with less than 2 nCi. Authors accounted for age, calendar year and induction times (two-year and five-year). Considering a two-year induction time, elevated rate ratios were observed for lymphopoietic cancers (RR 7.69, 90% exact CI 0.99-72.93), lymphosarcoma and reticulum cell sarcoma (RR 2.01, 90% exact CI 0.10-31.48), esophagus (RR 3.26, 90% exact CI 0.25-36.81), stomach (RR 1.84, 90% exact CI 0.20-14.40) and prostate (RR 3.74, 90% exact CI 0.29-42.31) (Wilkinson et al., 1987). With a five-year induction time, elevated rate ratios were observed for all causes (RR 1.33, 90% exact CI 1.05-1.68), lymphopoietic cancers (RR 9.86, 90% exact CI 1.26-94.03), lymphosarcoma and reticulum cell sarcoma (RR 2.50, 90% exact CI 0.12-39.57), esophagus (RR 3.68, 90% exact CI 0.29-41.56), stomach (RR 2.18, 90% exact CI 0.23-17.11), colon (RR 1.62, 90% exact CI 0.11-18.27), and prostate (RR 4.90, 90% exact CI 0.38-55.84) (Wilkinson et al., 1987). Finally, with a 10-year induction time, lung cancer was elevated (RR at 1.43, 90 % exact CI 0.33-4.65), although not statistically significant. Other findings included: elevated RR all causes (RR 1.39, 90% exact CI 1.04-1.87), all cancers (RR 1.39, 90% exact CI 0.88-2.93), lymphopoietic cancers (RR 5.22, 90% exact CI 0.57-38.80), esophagus (RR 1.46, 90% exact CI 0.34-4.77), stomach (RR 4.82, 90% exact CI 0.51-38.18), colon (RR 5.70, 90% exact CI 0.38-65.21), and prostate (RR 10.62, 90% exact CI 0.76-127.15) (Wilkinson et al., 1987).

The third part of the study compared workers with $\geq$ 1 rem of cumulative exposures to external radiation to those < 1 rem with a ten-year induction time. Elevated RRs were found for myeloid leukemia (RR 3.02, 90% exact CI 0.15-46.42), lymphosarcoma and reticulum cell carcinoma (RR 3.00, 90% exact CI 0.12-58.16), liver

neoplasms (RR 2.77, 90% exact CI 0.22-31.19), and unspecified brain tumors (RR 3.96, 90% exact CI 0.60-27.16) (Wilkinson et al., 1987).

In summary, no dose- response relationships were found for either plutonium or external radiation exposures. Overall results suggest that while some of the rate ratios were elevated, the confidence intervals were wide and comparisons were based on few cases.

A recent nested case-control study was conducted at the Rocky Flats site that examined lung cancer and cumulative internal radiation dose. Annual doses to the lung from plutonium, americium, and uranium isotopes were calculated for each worker with an internal dosimetry model. Lung cancer risk was elevated among workers with cumulative internal lung doses of more than 400 mSv in several different analytical models (Brown et al., 2004). A dose-response relationship was not consistent at high doses of internal radiation.

Rocketdyne/Atomics International, California

A retrospective, cancer mortality cohort study on 4,563 white male employees who were enrolled in the company's health physics radiation monitoring program between 1950 and 1993 were studied (average follow-up was 26.1 years). These employees were selected because they had been monitored for exposure to external radiation. Most external radiation monitoring involved whole-body doses of gamma and X-rays measured from film badges, thermoluminescent dosimeters, or pocket chambers. As a proxy for socioeconomic status, workers were assigned into one of three pay categories: hourly/union, salaried technical/administrative, managerial/professional (Ritz et al., 1999a). Results of comparisons made among U.S. white males demonstrated a healthy worker effect since the worker's mortality rates for all causes and for all cancers were lower, except for leukemia (SMR 1.6, 95% CI 0.95-2.52). It is postulated that the Rocketdyne/Atomic International (RAI) employees were better educated and had more

extensive health insurance than white males in the U.S. population (Ritz et al., 1999a). Internal comparisons were made using conditional logistic regression, comparing individuals who have died from cancer with those still at risk from cancer. Confounding from pay type, time since first monitoring, age at risk (continuous), and internal radiation (continuous) were included in all models. With a zero lag in exposure measurement, total cancer mortality was found to increase with cumulative external radiation dose (*P* for trend = 0.036) and a weaker trend was observed for all radiosensitive solid cancers (*P* for trend = 0.12) (Ritz et al., 1999a). Similar results were observed when cumulative radiation dose was lagged by 2-20 (models using 0, 2, 5, 10, 15, 20 years were examined) years. Radiosensitive solid tumors were grouped according to information from BEIR V and included cancers of the lung, esophagus, stomach, colon, brain, breast, urinary tract, thyroid, ovaries and bone (National Research Council, 1990).

A follow-up study was conducted to assess the effect of chronic exposure to internal radiation (primarily uranium, mixed-fission products, ^{90}Sr, ^{137}Cs and small amounts of plutonium) on cancer mortality (Ritz et al., 2000). Analyses focused on 2,297 employees involved in nuclear fuel assembly and disassembly operations who were monitored for internal radionuclide exposure from 1950-1994. Considering all the radionuclide exposures, a cumulative internal radiation dose was then estimated for each employee based on urinalysis, whole-body and lung counts reported for individual workers. When comparing the mortality experience of the male RAI workers to the white male U.S. population, there was a strong healthy workers effect: for all causes (SMR 0.72, 95% CI 0.66-0.80), and all cancers (SMR 0.87, 95% CI 0.73-1.03) (Ritz et al., 2000). By pooling cancers into one category (upper aerodigestive cancers), it was possible to perform dose-response analyses. Using dose-response analyses, associations were observed between cumulative internal dose and hematopoietic and lymphopoietic cancers (*P* for trend = 0.0001) and from cancers of the upper aerodigestive tract (*P* for trend = 0.0001) (Ritz et al., 2000). The corresponding rate ratios for

hematopoietic/lymphopoietic and upper aerodigestive tract cancers (naso-oropharyngeal regions, esophagus and stomach), comparing a cumulative dose $\geq$ 30 mSv with 0 mSv, was (RR 44.6, 95% CI 5.64-353) and (RR 57.2 , 95% CI 8.17-401) respectively.

A more recent study of 5,801 Rocketdyne workers who were monitored for radiation exposure examined mortality from all causes compared to the general population of California (Boice, 2006). Cox proportional hazards models were also used to evaluate dose-response trends over cumulative radiation dose (combining external and internal organ-specific radiation doses). In order to minimize healthy worker effect, internal comparisons were made when evaluating the dose-response relationships. The nonexposed referent category was comprised of Rocketdyne workers not monitored for either external or internal radiation. Results indicated a SMR of 0.93 (95% CI 0.84-1.02) for all-cancer mortality and SMR of 1.21 (95% CI 0.69-1.97) for leukemias (excluding CLL) (Boice, 2006). Similarly, Cox regression analyses failed to show any significant dose-response trends for any type of cancer.

A recent mortality study was conducted among 8,372 Rocketdyne workers who tested rocket engines (Boice, 2006a). There is a 2668-acre site at the boundary of Los Angeles and Ventura counties where 11 major rocket engine and component test areas were established. During the testing of rocket engines, there was potential exposure to a wide range of engine fuels, solvents, hydrazine-based fuels, and trichloroethylene (TCE) (Boice, 2006a). Results showed no consistent associations between cancer and chemical exposures associated with the testing of rocket engines between the years 1948-1999. Non-significant associations were demonstrated between renal cancer and TCE, lung cancer and hydrazines, and stomach cancers and years worked as a test stand mechanic (Boice, 2006a).

Pantex Plant, Amarillo, TX

This facility's functions include the assembly of conventional high explosive and nuclear materials into nuclear weapons, maintaining and testing existing nuclear weapons, disassembling these weapons, and performing related research and development (DOE, 1999). Studies of Pantex workers are particularly relevant to this present study because production processes transferred from IAAAP to Pantex in 1975. Both IAAAP and Pantex workers were involved in similar production processes and were managed by the same contractor. There are some radiation data available from Pantex and IAAAP that suggest that monitored Pantex workers may have had greater maximum individual doses than the IAAAP workers (see Table 1.5).

An initial mortality study from 1951-1978 of Pantex workers suggested a strong healthy worker effect overall, but non-significant elevations were observed for leukemia and brain cancer (Acquavella, et al., 1985). This retrospective cohort study consisted of 3,564 white males ever employed from 1951 and 1978 (length of follow-up averaged 14.6 years). Workers may have been exposed to low-level external radiation (gamma or neutron), industrial radiographic equipment (x ray) and other chemicals used in high-explosive fabrication (i.e. solvents) (Acquavella et al., 1985). Cumulative whole-body radiation doses were estimated using film-badge measurements which were available for workers employed after 1963. There were significantly fewer deaths than expected from all causes of death (SMR 0.72, 95% CI 0.64-0.81), all cancers (SMR 0.60, 95% CI 0.44-0.81), digestive cancers (SMR 0.43, 95% CI 0.18-0.84), lung cancer (SMR 0.49, 95% CI 0.25-0.86), arteriosclerotic heart disease (SMR 0.75, 95% CI 0.61-0.91) and digestive disease (SMR 0.46, 95% CI 0.22-0.85) (Acquavella et al., 1982 and 1985). A relative standardized mortality ratio (RSMR) was calculated by dividing each cause specific SMR by the total mortality SMR. Non-statistically significant elevations were found for leukemia (RSMR 1.28, 95% CI 0.48-4.55), brain cancer (RSMR 1.89, 95% CI 0.51-4.83) and all lymphopoietic cancer (RSMR 1.18, 95% CI 0.47-2.44) (Acquavella et al., 1985).

A recent follow-up retrospective mortality study included 4,668 males and females of all races ever employed at the Pantex facility between 1951 and 1978. Cause of death was collected on former employees who had died prior to 1995. SMR analyses were performed on two cohorts of workers: the full NIOSH cohort and a smaller early-term cohort. The early-term cohort was a sub-set of the full NIOSH cohort and had more complete work history information available. Analyses involving duration of employment and lag periods were performed on the early-term cohort.

The full NIOSH cohort continued to indicate a strong health worker effect; mortality from all causes (SMR 0.81, 95% CI 0.76-0.86), all cancers (SMR 0.78, 95% CI 0.69-0.88), which were both significantly lower than the U.S. population (Silver et. al, 2005).

The early term cohort demonstrated a higher all cause mortality (SMR 0.98, 95% CI 0.92-1.05) and a higher all cancer mortality (SMR 0.86, 95% CI 0.74-1.0) than the full NIOSH cohort and was close to that expected from the U.S. population rates (Silver et. al, 2005).

Cause-specific analyses were also performed on both cohorts. Ischemic heart disease was significantly lower in both the full NIOSH cohort (SMR 0.70, 95% CI 0.62-0.79) and the early term cohort (SMR 0.81, 95% CI 0.70-0.94) (Silver et. al, 2005).

Additional analyses performed on the early term cohort included SMRs (stratified on duration of employment) and Standardized Rate Ratios (SRR) using lag periods. For multiple myeloma (SMR 2.09, 95% CI 0.76-4.55) with a 10-year lag, the exposure-responses were also positive and statistically significant at p<0.0001 with 10-year lag (SRR 1.16) and 15-year lag (SRR 1.49) (Silver et. al, 2005). Prostate cancer had only a slightly elevated SMR, but the SRRs showed statistically significant positive exposure responses at p=0.0016 with 10- year lag (SRR 1.60) and 15-year lag (SRR 2.14) (Silver et. al, 2005).

Lawrence Livermore National Laboratory, Alameda

County, California

The Lawrence Livermore National Laboratory (LLNL) is a high-energy physics laboratory in California. An initial study in 1981 detected a fourfold excess incidence of malignant melanoma among employees (Austin and Reynolds, 1981). A follow-up cancer incidence study in 1984 consisted of all active LLNL employees between the ages of 20-69 who resided in the San Francisco-Oakland Standard Metropolitan Statistical Area (SMSA) between 1969 and 1980. Expected cancer cases were calculated using the same sex and age statistics from the San Francisco-Oakland SMSA population. Observed cases were ascertained from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program which maintains a registry in the area since 1969. Results indicated that the overall cancer incidence is approximately that for the general population. However, an excess incidence of melanoma, rectal and salivary gland cancers among women was detected. Men had an excess incidence of malignant melanoma and a deficit of lung cancer. The author suggests that the elevated risk of site-specific cancers in women may be due to chance, but the elevated melanoma risk, SIR of 5.19 in women, may represent an actual excess of cases (Reynolds and Austin, 1985).

Multi-Site Studies

Since the statistical power of individual cohorts has been low, combined analyses of selected cohorts have been performed. In the United States, pooled analyses of data from the Hanford Site, Oak Ridge National Laboratory (ORNL) and Rocky Flats Nuclear Weapons Plant increase power and provide tighter confidence intervals on risk estimates. The study population of the combined cohort consisted of 44,943 white male workers employed by one of the three plants for at least six months. Workers from all three facilities were monitored for external radiation exposure through dosimeters and estimates of the whole-body dose were available for each year of monitoring (Gilbert et

al., 1989b). Results of the combined analyses showed no evidence of a correlation between radiation exposure and mortality from all cancer or from leukemia (Gilbert et al., 1989b). There was a statistically significant positive association with radiation and multiple myeloma but this was entirely due to the correlation previously described in Hanford workers (Gilbert et al., 1989a and 1993a). Updated analyses that included more recent mortality data from the individual cohorts did not show a positive correlation between radiation exposure and mortality from all cancer or from leukemia (Gilbert et al., 1993b).

A recent mortality study of 8,976 former construction and craft workers employed at Hanford Nuclear Reservation, Savannah River Reservation, Amchitka Site, and Oak Ridge Reservation was performed on former workers who signed up for a DOE medical surveillance screening program from 1996 to 2004. Excess mortality for all cancers (SMR=5.93, 95% CI 2.56-11.68), lung cancer (SMR=5.93, 95% CI 2.56-11.68) and mesothelioma (SMR=5.93, 95% CI 2.56-11.68) (Dement et al., 2009).

Combined international studies have been conducted of nuclear industry workers from United States, Canada and United Kingdom (UK). Mortality data for 95,673 workers (85% men) monitored for external exposure to ionizing radiation (primarily gamma radiation) and employed for 6 months or longer were analyzed (Cardis et al., 1995). This study combined mortality data from seven previously published studies: Hanford, Rocky Flats, Oak Ridge National Laboratory, Sellafield (UK), Atomic Energy Authority (UK), Atomic Weapons Establishment (UK) and Atomic Energy of Canada Ltd. Results indicated no evidence of an association between radiation dose and mortality from all cancers (excluding leukemia) or all causes (Cardis et al., 1995). Mortality from leukemia (excluding chronic lymphocytic leukemia) was significantly associated with cumulative radiation exposure (one-sided P value=0.046) with a significant ERR as well, 2.18 per Sv (90% CI 0.1-5.7) (Cardis et al., 1995). There was also a significant association between multiple myeloma and radiation dose (one-sided P

value=0.037) and ERR was 4.2 per Sv (90% CI 0.3-14.4) (Cardis et al., 1995). The significant association between radiation dose and multiple myeloma was due to the number of deaths at the Hanford and Sellafield facilities, reflecting analyses performed previously (Gilbert et al., 1993a and Smith et al., 1986)

A much larger multinational retrospective cohort study of nuclear facilities (154 total) located in 15 countries was recently published (Cardis et al., 2007 and Vrijheid et al., 2007). Countries included in the study were: Australia, Belgium, Canada, Finland, France, Hungary, Japan, South Korea, Lithuania, Slovak Republic, Spain, Sweden, Switzerland, UK, and USA. The main study population consisted of 407,391 workers (90% men) who received an average cumulative dose of 19.4 mSv (90% of workers received cumulative doses <50mSv and less than 0.1% received cumulative doses >500 mSv) (Cardis et al., 2005). To be included in the study, a minimum set of variables was required for each cohort member: date of birth, sex, socioeconomic status, vital status, date and cause of death, employment history, and dosimetric information. Information collected on socioeconomic status was country-specific and based on job title and/or on education level (Vrijheid et al., 2007). Results indicated a significantly elevated risk of all cancers (excluding leukemia) and elevated risk of leukemia (excluding CLL). Estimated relative risks were 0.97 per Sv (95% CI 0.14-1.97) and 1.93 per Sv (95% CI <0 to 8.47) respectively (Cardis et al., 2007). To address confounding due to smoking separate analyses were performed on lung cancer, other smoking-related cancers and non-malignant respiratory diseases. The only significant association was between average cumulative dose of radiation and lung cancer, 1.86 per Sv (95% CI 0.26-4.01) respectively (Cardis et al., 2007). This finding suggests that the significant relationship between external radiation and increased risk of all cancers is not entirely due to cancers related to smoking.

Table 1.1 Timeline of AEC Operations and Pertinent Events at IAAAP 1940-1975

DATE	EVENT
1940 November	Contract with Day & Zimmerman approved
1941 January	Plant construction begins
1941 September	Line 1 loading operations begin (non-nuclear)
1941 November	Line II loading operation begin (Army side)
1941 December	Line III operations begin
1941 December 12	Explosion in building 1-05-1 of Line 1
1942 January	Lines IV-A and IV-B begin
1942 March	Explosion in building 3-05-1 of Line III
1943	Line III-A begins
1945-1951	Increased production and recruitment at plant due to Korean War
1947	Iowa Ordnance Plant converted to a weapons assembly plant. Functions were previously performed at Sandia Base. IAAAP and Pantex perform primarily nuclear weapons assembly functions from 1951-1975.
1947	Complete rehabilitation of Line 1 for AEC work
1947-1975	Plant produces high explosives main charges for nuclear weapons
1949	Silas Mason Co. accepts responsibility for operation of highly classified Division B facilities (AEC)
1951	Silas Mason Co. accepts responsibility of operations for all shell, bomb and component lines
1952 December	Division B production peaks
1953	Korean War cease-fire and major plant-wide reduction of employees
1958 June	Explosion Line II, building 2-10
1963	AEC takes over Division B from Silas Mason Co
1975	IAAAP transfers to Pantex in Texas

Table 1.2 Units of Radiation Dose (modified from BEIR VII Manual, 2005)

Unit	Symbol	Conversion Factors
Becquerel (SI)	Bq	1disintegration/s= 2.7×10^{-11} Ci
Curie	Ci	3.7×10^{10} disintegration/s = 3.7×10^{10} Bq
Gray (SI)	Gy	1 J/kg = 100 rads
Rad	rad	0.01 Gy = 100 er/g
Sievert (SI)	Sv	1 J/kg = 100 rem
Rem	Rem	0.01 Sv

Table 1.3 Type of Radiation and Energy Range

Radiation Type and Energy Range	Radiation weighting factor (Q-factor)
Photons (x-rays, gamma rays)	1
Electrons (beta particles)	1
Neutrons by energy:	
< 10 keV (kilo electronvolt)	5
10-100 keV	10
>100 keV to 2 MeV	20
2-20 MeV (Mega electronvolt)	10
>20 MeV	5
Protons, other than recoil protons, > 2 MeV	5
Alpha particles, fission fragments, heavy nuclei	20

Source: modified from the International Commission on Radiological Protection (ICRP). Smith, H. Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Ann ICRP 1991; 21:1-3.

Table 1.4 Commonly Encountered Radionuclides

Radionuclide	Half-Life	Typical source of Exposure	Emissions	Target Organ
Tritium (^{3}H)	12.3 yrs	Biomedical research, nuclear weapons, power plants	Beta	body water
Strontium (^{90}Sr)	27 yrs	Nuclear fallout	Beta	Bone
Technetium (^{99}Tc)	6 hr	Medical diagnosis	beta, gamma	None
Iodine (^{131}I)	8 days	Medical diagnosis and therapy	beta, gamma	Thyroid
Cesium (^{137}Cs)	30 yrs	Radiation sources	Gamma	Bone
Radon (^{222}Rn)	3.8 days	Indoor environment, mines	Alpha	Lung
Uranium (^{238}U)	4.5 billion yrs	Weapons production	alpha, beta	lung, kidney
Plutonium (^{239}Pu)	20,000 yrs	Weapons production, reactors	Alpha	Lung

Source: modified from Claycamp HG and Wald N. Radiation. In: Rosenstock L, Cullen MR, Brodkin CA, eds. Textbook of Clinical Occupational and Environmental Medicine. Philadelphia: Elsevier Saunders, 2005;857.

Table 1.5 IAAAP External Radiation Doses 1955-1975 compared to Pantex Plant

Year	IAAAP Maximum Individual Dose (mRem)	IAAAP Individuals Monitored N	Pantex Maximum Individual Dose (mRem)	Pantex Individuals Monitored N	Pantex Average Worker Dose (mRem)
1955	40	3	0	1	0
1956	NA	0	0	1	0
1957	NA	15	20	3	10
1958	145	18	49	19	5
1959	5	12	75	22	20
1960	91	12	848	69	150
1961	80	0	831	71	120
1962	90	36	342	64	80
1963	90	0	2654	218	80
1964	60	66	4410	253	320
1965	90	45	3690	416	110
1966	80	70	2750	581	120
1967	80	61	3330	563	140
1968	90	162	1200	423	70
1969	950	203	2850	432	70
1970	960	274	2787	468	180
1971	900	354	3560	495	210
1972	90	372	2950	467	150
1973	220	330	6550	441	200
1974	70	191	5060	500	150
1975	30	42	10800	493	130

Source: Field RW, unpublished and unverified radiation records from IAAAP AEC/DOE workers.

Fix JJ, Trom DJ, Traub RJ, et al. PantexPlant-Occupational External Dose, 2007.
ORAU Team Dose Reconstruction Project for NIOSH. Document Number: ORAUT-TKBS-0013-0.

Table 1.6 Summary of Statistically Significant Mortality Findings Among DOE Sites, (Significantly Decreased=D and Significantly Elevated=E)

DOE Site	All Cause Mortality	Cancer Mortality
Oak Ridge National Laboratory, X-10	D	E
Oak Ridge National Laboratory, Y-12		D
Oak Ridge National Laboratory, K-25	E	
Hanford		E
Fernald Feed Materials Production		
Mallinckrodt Chemical Works		
Savannah River Site		
Linde Air Products	E	
Mound Laboratory		
Los Alamos National Laboratory		
Zia Company	E	E
Rocky Flats	E	D
Rocketdyne/Atomics International	D	E
Lawrence Livermore National Laboratory		
Pantex Plant	D	D
Multi- Site*		E
Multi- Site**		
15-Country Study		E

Note: Multi-Site* includes: Hanford Nuclear Reservation, Savannah River Reservation, Amchitka Site, and Oak Ridge Reservation.

Multi-Site** includes: Hanford, Oak Ridge National Laboratory and Rocky Flats.

Table 1.7 Summary of Statistically Significant Cause-Specific Mortality Findings Among DOE Sites, (Significantly Elevated=E)

Cause-Specific Mortality	ORNL X-10	ORNL Y-12	ORNL K-25	Hanford	Fernald	Mallinckrodt	Savannah	Linde	Mound	Los Alamos	Los Alamos (Zia)	Rocky Flats	Rocketdyne	Pantex	Lawrence
Oral Cavity/Pharynx															
Lip															
Brain										E					
Thyroid												E			
Esophagus										E					
Stomach					E						E				
Liver and Gallbladder				E	E										
Pancreas															
Urinary Bladder															
Kidney										E					
Melanoma															
All Respiratory			E												
Larynx					E										
Laryngeal								E							
Lung and Bronchus		E		E								E	E		
Pleura (Mesothelioma)							E								
Female Breast															
Colon															
Rectum															
Ovary															

'Table 1.7 continued'

Cause-Specific Mortality	ORNL X-10	ORNL Y-12	ORNL K-25	Hanford	Fernald	Mallinckrodt	Savannah	Linde	Mound	Los Alamos	Los Alamos	Rocky Flats	Rocketdyne	Pantex	Lawrence
Cervix															
Uterus															
Lymphatic/ Hematopoietic				E					E	E		E	E		
Leukemia							E		E				E		
AML															
CLL															
CML															
Other Leukemia															
Multiple Myeloma			E	E											
Hodgkin Lymphoma				E						E					
Non-Hodgkin Lymphoma															
Other Cancers															
Respiratory Diseases			E					E			E				
Pneumonia			E					E							
COPD															
Circulatory Disease								E			E				
Heart Disease															
Arteriosclerotic disease								E							
Diabetes Mellitus															

'Table 1.7 continued'

Cause-Specific Mortality	ORNL X-10	ORNL Y-12	ORNL K-25	Hanford	Fernald	Mallinckrodt	Savannah	Linde	Mound	Los Alamos	Los Alamos	Rocky Flats	Rocketdyne	Pantex	Lawrence
Psychiatric Disorders			E								E				
Injuries											E				

CHAPTER TWO: METHODS

Preliminary Studies

Currently, the University of Iowa, College of Public Health is in the process of a congressionally-mandated study of the health risks of non-AEC workers at the IAAAP. Historically, two groups of workers were employed at the IAAAP, one large group worked under the authority of the Department of Defense (DOD), and another smaller group under the AEC. This study focuses on the approximately 5,743 AEC workers formerly employed at the IAAAP plant in Middletown, Iowa between the early 1940s and 1975. The government-owned IAAAP was built between 1941 and 1943 in order to manufacture munitions needed for WWII. This 19,000-acre facility is located in Middletown, Iowa and is comprised of over 1,000 buildings. Conventional missile warheads and a variety of large caliber tank ammunitions, mines, mortars, artillery, demolition charges, and weapons' components have been produced at the facility. In 1947, it was designated as the first plant in the nation to assemble atomic weapons, which were manufactured in an area designated as Line 1. Line 1 manufactured nuclear weapons until 1975 when production was transferred to Pantex, TX.

A previous needs assessment (Fuortes 2001) has documented that the IAAAP AEC workers were potentially exposed to the following toxicants: TNT 2,4,6-Trinitrotoluene; RDX Cyclonite; Hexahydro-1,3,5-trinitro-1,3,5-triazine; HMX Octahydro-1,3,5,7 tetranitro-1,3,5,7-tetrazocine; Tetryl Tetranitromethylaniline; Explosive Melts (Composition B, Baratol, Cyclotol and Boracitol); MOCA 4,4-Methylene bis (2-chloroaniline); Asbestos; Silica; Depleted Uranium (nephrotoxin); Organic solvents; Uranium-238; Uranium-235; Plutonium-239; Tritium; and various radiographic x-ray sources.

Film badges were used to monitor about 15% of the AEC workers for external ionizing radiation primarily from uranium-235 and plutonium-239 and their radioactive

decay products. Bioassays were also performed to monitor for internal deposition of radionuclides (e.g., tritium, uranium, etc.). Film badge data are available and indicate that except in rare cases yearly allowed radiation exposures were not exceeded for monitored workers. However, bioassay data are not available.

Construction of Cohort

We acquired former AEC worker data from the IAAAP on the former AEC employee cohort that were available in the form of personnel 3" x 5" index cards. These personnel cards were developed primarily to track terminations from 1941 through 1975. Most of the personnel cards contain date of hire, date of termination, pay rate and specific job code. There are cards with multiple job codes and are believed to reflect the entire employment history of individual workers. The cards were scanned, double-entered and are maintained on a secured SQL server unique to the University of Iowa DOD/AEC study.

These records have allowed identification of a cohort of 5,743 former workers who met criteria as having worked for the AEC between 1947 and 1975. Preliminary confirmation of vital status was determined by Social Security Administration (SSA) linkage resulting in 4,094 workers deceased and 1,649 living members of the cohort. Radiation records of external radiation have been double-entered for approximately several hundred former workers, but QA/QC checks have not been performed on these records to date.

Cohort Identification

Inclusion criteria for the cohort was defined as anyone appearing employed on the cards, with an AEC job classification, for at least a three-month period between January 1, 1947 and December 31, 1975. The vital status of all workers who met those criteria was obtained through December 31, 2005.

The data set was checked for accuracy and completeness against Employer Identification Social Security Summary Earnings Report selected for various time periods after 1970. Employment at the plant was verified by linking employee's name, Social Security Number to the IAAAP employer identification number. Job codes and work histories that are unique to AEC workers were also reviewed. All workers with AEC-identified job codes, employee identification number or self-reports indicating exposures to Line 1 or AEC processes were included in the cohort. The above linkages together with the workers' employment history has identified most of the cohort of interest and thus allowed for an unbiased sampling.

<u>Job Dictionary and Work History</u>

A comprehensive job dictionary has been developed that includes all AEC/DOE job titles used at IAAAP. The final job dictionary includes: job title, job code, department, and brief description of duties. The sources of job titles and/or job codes have been obtained from the following sources.

Personnel note cards (IAAAP termination data): personnel cards archived at the plant were used by IAAAP contractors Silas Mason, Mason Hangar, and American Ordnance to track terminations of both DOD and AEC/AEC employees from 1947-1993. Nearly all bargaining and non-bargaining IAAAP employees during this period were assigned cards that list name, SSN, badge number, job code (alphanumeric designation specific to a given job title), and termination date for that particular tenure of employment. Many employees have multiple cards, indicating several periods of employment and/or movement between jobs ranks. Most cards include hire dates in addition to termination date for an employment period, as well as other codes associated with pay rates, departments, or time clock. Because some cards are incomplete or employees have more than one card, other sources of data (Union contract books and SSA data) were used in order to construct the most complete work history possible.

Union contract booklets and log books: IAAAP maintains copies of annual union contract booklets that provide job titles and pay grades for bargaining positions in the 11 unions whose members worked at the plant from 1951 to the present. Approximately 2/3 of current workers are covered by bargaining positions; a higher proportion is evident for early years at the plant based on review of card and electronic data. Non-bargaining positions include administration, professional, and supervisor positions. Log books provide additional information linking specific job codes with titles, as well as names of bargaining employees covered by specific titles and historic information on what codes/titles existed or changed annually. Historical linkage between job code and title available in the log books supplemented job codes found in card data.

IAAAP radiation records: radiation sampling records are available for 15% of the AEC/DOE employees and were reviewed for additional information on date of monitoring, job task and job title. Preliminary examination of IAAAP radiation records (see Table 1.5) demonstrated that monitored employees were exposed to levels of external radiation well below 5 rem (the current occupation limit).

Social Security Administration data: SSA data from 1951-2005 was reviewed to cross-check the hire (start) and termination (end) dates. If an end date was missing on an employee's personnel card, the SSA quarterly employment data was used to impute the dates (see section Determining Start and End Dates).

<div align="center">Determining Vital Status: Data Sources</div>

Multiple databases were utilized to determine vital status, race, gender, date of birth, date of death, length of employment, etc. Table 2.1 displays the multiple sources of data available and the specific information obtained from each one. The AEC/DOE employees are older and less electronic information was available as compared to the DOD cohort. For instance, LexisNexis provides more accurate information after 1985 as compared to earlier years when individuals were not using credit cards. Some of the

most important data were retrieved from the employee records, which were obtained

from the handwritten personnel cards. There were often discrepancies discovered with

the employee's name, social security number, or date of birth, usually observed as

linkages to Social Security data were attempted. Women were more difficult to trace

because some would change names with marriage or in rare cases use their husband's

social security number during employment.

Since multiple data sources were used, a step-by-step process to retrieve this

information was used. Finding information on the living and deceased members of the

cohort involved focusing on certain data sources. A hierarchy of data sources was

developed and SSA data were considered the prime source. This step-by-step process

was used for searching for certain variables of interest, i.e. race, sex, date of birth, date of

death, state of residence, etc. Figure 1 delineates the steps involved in finding missing

information on the *living* members of the cohort using name and SSN. For living

members, we would start by searching in the SSA Vital Status data then search the Iowa

Driver's License data, and finally search the LexisNexis data. Figures 2-6 displays the

steps in finding information on the *deceased* members. For deceased members, we

verified death from the SSA Vital Status data and then queried NDI data if the death was

after 1979 or requested individual state death certificates if it was earlier than 1979. We

then continued on to the Iowa Driver's License data, the SSA Death Master Files and

finally LexisNexis data to find missing information.

<u>Determining Start and End Dates</u>

One challenge in determining the duration of employment and the amount of

person-years to apply to each employee was the lack of start and end dates for each

person. Of the 5,743 AEC/DOE former employees, about 47% were missing their start

date at the plant. The start and end dates were determined from the personnel 3" x 5"

index cards. These personnel cards were developed primarily to track terminations from

1941 through 1975. See Tables 2.2, 2.3 and 2.4 for summary information on the missing dates. In order to account for the missing dates, a decision tree was developed that ordered a step-by-step process in which to impute the missing information (See Figure 7). If a former worker had an EIN number but no start or end date then he/she was given one year of employment.

If a worker had no start date but had an end date then the start date was estimated by using the job code start date. The job code start date was identified through the job dictionary. For those workers with no start dates, who do have end dates, but have no job code, then a start date of 1947 was assigned. Duration of employment was calculated by averaging the years worked. For example, most workers have end dates in the early 1950s. If a worker was assigned a start date of 1948 and has an end date of 1952, then the worker was given half of the years worked, two years total. This method may underestimate the years worked but it is the most conservative estimate.

For those workers with no start dates who have end dates after 1958 (N=14) then job code was used to estimate duration of employment.

Determination of Vital Status

One of the challenges in occupational cohorts is confirming "living" status among employees who are separated from IAAAP. Vital status information for the cohort was accomplished by linking cohort members' personal identifiers with data compiled in national and/or regional databases. The Social Security Administration (SSA) provides information on vital status data by comparing social security numbers of the cohort with individuals who have made social security payments or are receiving benefits (still alive). The names and social security numbers from the AEC employment records were cross-checked against SSA Summary Earning Reports for accuracy of social security number and earning history. Next, the personal identifiers of the former workers were submitted to the SSA to obtain both plant-specific yearly earning information, based on employer

identification number (EIN), available after 1970 and information on all sources of income prior to 1970. Information on gender and race was also obtained from this special SSA inquiry.

Further demographic information was verified through a LexisNexis inquiry, a nationwide person locator database which provided complete histories on subjects' current and previous surnames along with associated dates from 1980 onwards. Some partial histories are available prior to 1980 but information is limited. LexisNexis uses Social Security Number, name and birth date to find current and previous addresses with associated dates.

To further assess residential histories in Iowa and verify personal identifiers, the Iowa Department of Motor Vehicles databases from 1985, 1993, 1999 and 2005 were evaluated. Records were linked using name and birth date.

For any remaining unknown vital status information, a conservative approach was used by assuming the individual is alive. If there was no death indication for a worker and they were confirmed to be alive as of January 1, 1979 (start of NDI) or later by the SSA then they were assumed to be alive as of December 31, 2005. Those lost to follow-up before January 1, 1979 were only considered alive until the date last observed. This assumption could only bias results towards the null on the assumptions that some individuals may have changed names, migrated outside the U.S. or have no federal records, but may nevertheless have died.

<u>Determination of Cause of Death</u>

Deceased employees' personal identifiers were submitted to the CDC National Center for Health Statistics, National Death Index (NDI *Plus*) to ascertain cause of death (COD) and underlying cause of death (UCOD). The CDC's NDI data, received from the states' offices of vital records, dates back to 1979. The NDI consists of all death records from the fifty states, the District of Columbia, Puerto Rico and the Virgin Islands. These

combined records form a central, computerized index of death record information for the U.S. Data received include first and last names, father's surname, SSN, date and state of birth, state of residence, sex, race, marital status, and age at death (Cowper et al., 2002).

If a death occurred before 1979, the date and state of death were identified through the SSA. We subsequently requested paper copies of death certificates from the relevant states for deaths that occurred before NDI started.

The vital records department was contacted for each state where workers are known to have died and necessary paperwork was filed. We are continuing to collect copies of death certificates from the states' Bureau of Vital Statistics for workers who died between 1951 and 1979. State death certificates commonly contain date of birth, date of death, COD and UCODs.

To maintain consistency of coding, the paper copies of death certificates obtained from other states for the above period were reviewed by an experienced subcontracted nosologist recommended by the National Center for Health Statistics (NCHS). The nosologist coded the underlying cause of death (UCOD) and each listed cause of death for each decedent according to the International Classification of Diseases ICD-7 to ICD-10. The ICD code applied was determined by the code that was in use when the person died so that the results are more generalizable to the reference population.

<div align="center">Determination of Cancer Incidence</div>

The cancer incidence cohort is a sub-set of the overall IAAAP mortality study. Inclusion into this portion of the study was determined if the IAAAP AEC/DOE employee was in the state of Iowa at the time of his/her cancer diagnosis. Employees must have worked at the plant between 1947 and 1975 and lived in Iowa at any time between 1969 and 2005. Residential histories of subjects included in the incidence study were gathered using SSA, LexisNexis and DMV linkages. If there is no postemployment

residential history for a subject then it was assumed that the employee left Iowa at the date of last employment.

Cancer incidence was determined through the State Health Registry of Iowa (SHRI). The SHRI is a statewide, population-based cancer registry that has been collecting data since 1969 and participated in the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program since 1973. Iowa cancer incidence data from 1972 are not available. Eligible AEC/DOE employees were matched by SSN and partial/full name to the SHRI. A case was counted if the subject's diagnosis occurred after 1969 (no cancer records for 1972), had an Iowa residential history at time of diagnosis and had started work as an AEC/DOE worker before diagnosis.

Calculation of Person-Years

Each member of the mortality cohort accumulated person-time from the date of entry (completion of 90 days of employment) until the earliest of the following: the date of death for deceased workers, the date last observed for persons lost to follow-up or the ending date of the study (December 31, 2005).

Person-years accumulation for sub-set of workers in the cancer incidence cohort started in 1969 and continued until the earliest of the following: the date of death for deceased workers, the date of cancer diagnosis, the date last observed for persons lost to follow-up or the ending date of the study.

Software

Mortality and incidence data were analyzed using the National Institute of Occupational Safety and Health (NIOSH) Life Table Analysis System (LTAS) software. The NIOSH Life Table was created primarily to analyze cohorts defined by occupational exposures. It therefore requires input of a history file in order to calculate cumulative exposure or duration of employment or exposure. The system also requires a person file containing demographic information and an Outcome file containing data on observed

events (deaths or disease incidences). LTAS then generates rates by age, race, sex and calendar time, where rates are calculated as observed events divided by person-time at risk in the interval. In addition, LTAS allows for cross-stratification by time since first exposure/employment (TSFE) to account for latency, and by either duration of exposure or cumulative level of exposure to examine exposure/disease relationships.

Analysis by Specific Aim

AIMS 1 and 2: Compare the mortality rates for the former IAAAP AEC worker population as compared to reference populations.

- Determine if the overall mortality rate is higher in the IAAAP workers as compared to either the mortality rates for the U.S. population or state of Iowa.

- Determine if the cause-specific mortality rate is higher in the IAAAP workers as compared to the cause-specific mortality rates for the U.S. population or state of Iowa.

- Determine whether there is excess mortality in the cohort for causes of death known to be associated with smoking.

Standardized Mortality Ratio

Standardized mortality ratios (SMRs) for all causes of death (total mortality) were calculated. The SMR was calculated as the ratio of observed to expected events stratified for age (five year categories), gender, and five-year calendar period. Indirect standardization compares observed deaths within each stratum with expected deaths, where expected deaths are computed by multiplying the referent population death rates (stratified appropriately) by the observed person-years at risk in the stratum. The observed and expected deaths are then summed across all strata, and the SMR is the ratio of total observed deaths to total expected deaths for the cause of death category considered. Thus, the SMR compares the observed number of deaths in the cohort with

an expected number obtained by applying the standard rates to the cohort age structure (Breslow and Day, 1987). The basic formula:

$$SMR = \sum_i W_i R_{i1} / W_i R_{i0}$$

$R_{i1}=$ the stratum-specific rate in the AEC/DOE cohort.

$R_{i0}=$ the stratum-specific rate in the reference population (Iowa or U.S.).

$W_i=$ stratum-specific person-years in the AEC/DOE cohort.

The NIOSH Mortality Database Program was used to maintain data files and the Life Table Analysis System (LTAS) developed by the National Institute for Occupational Safety and Health (NIOSH) was used to obtain the SMR. Several methods are available to test for statistical departures of SMRs from 1.0. We computed a chi square test with one degree of freedom. It was assumed that the observed number of deaths from a particular disease followed a random, or Poisson distribution in time. The 95% CI was used to measure the statistical variability of the SMR.

Based on previous mortality studies of nuclear workers and known exposures possibly occurring at the plant, endpoints of interest include: all-cause mortality, all-cancer mortality and cause–specific mortality. Types of cause-specific mortality that were investigated included: heart disease, lung disease, liver disease, kidney disease, anemia and bone marrow failure. Cause-specific cancer endpoints include: renal, lymphomas (other than Hodgkin lymphoma), larynx, thyroid, breast, pancreas, small intestine, urinary bladder, brain, colon, ovary, lung, bone, bronchus, oral cavity, pharynx, trachea, sinus, liver, and leukemia.

Two comparison groups: the U.S. population and the Iowa population were used. The U.S. population is the customary choice for a reference population because the stratum-specific rates are generally stable, and thus expected numbers of the SMR can be considered as virtual constants (Gardner, 1986). However, using disease rates from the Iowa population is advantageous because it better represents the experience of the source population for the workers of IAAAP. If there is considerable geographic heterogeneity

of disease rates within the U.S., it is useful to choose the Iowa general population for a more regional comparison group (Checkoway et al., 2004).

Since there are no records available to assess the health effects of smoking, an indirect approach was used. Using the Iowa population as the reference group, SMRs were calculated for diseases known to be associated with smoking, i.e. non-malignant respiratory diseases (emphysema and bronchitis) and cardiovascular disease. If an exposed cohort has smoked substantially more than the Iowa population, then all the smoking-related diseases should be elevated (Steenland et al., 1984). For example, if an SMR is elevated for lung cancer but not for emphysema then the excess mortality is less likely due to the effects of smoking in the exposed population. If a healthy worker effect (HEW) is suspected, it should be particularly apparent at a greater magnitude for older workers employed less than 10 years (Arrighi and Hertz-Picciotto, 1994). By stratifying on variables such as, time since first employment, and/or length of follow-up, the effect of HWE should be reduced. Lower mortality rates for the workers may also in part be an artifact related to incomplete follow-up, erroneous information, and failure to obtain the cause of death for all workers.

AIM 3: Determine whether former IAAAP AEC workers experience higher site-specific cancer incidence rates as compared to a reference population from the state of Iowa.

Two major methodological challenges in conducting the cancer incidence study are: 1) correctly enumerating person-years at risk within the Iowa Cancer Registry's catchment area, and 2) the impact of workers who left the Iowa catchment area and developed cancer. We will use the following linkages and tracing procedures to enumerate person-years at risk: 1) listing of addresses for current workers, 2) match of Iowa Department of Motor Vehicle records for former workers, 3) the NDI will be examined for ICD codes (reflecting cancer to obtain an estimate of number of individuals outside of Iowa not accounted for using the State Health Registry of Iowa), and 4) Social

Security Summary Earnings Reports after 1970. To correctly enumerate the denominator, SSA Summary Earnings report will determine if former employees of retirement age reside and are receiving benefits in Iowa.

Proportional Incidence Ratio

The Proportional Incidence Ratio (PIR) was calculated first as a rough measure of the effect of AEC/DOE cohort membership on cancer incidence after 1969. The PIR compares the fraction of cohort incident cancer cases with the corresponding fraction from the Iowa population. The PIR may provide information on unusual patterns of incidence that should be followed-up with more traditional analyses.

PIRs for specific cancer sites were calculated as follows (Breslow and Day,

1987): $$PIR = \sum d / \sum t (d^* / t^*)$$

d= the number of incident cancer cases of a *specific site* in the AEC/DOE cohort.

t= the number of incident cancer cases of *all sites* in the AEC/DOE cohort.

d*= the number of incident cancer cases of a *specific site* in the Iowa population.

t*= the number of incident cancer cases of *all sites* in the Iowa population.

Standardized Incidence Ratio

The Standardized Incidence Ratio (SIR) was used as the measure of effect for the cancer incidence analyses. The SIR will be calculated as the ratio of observed to expected events with adjustment for five-year age categories, gender, and five-year calendar period. Expected incident cases was calculated by summing the product of the number of employee person-years, stratified by age, calendar period, and gender, and applying rates for the corresponding groups in the Iowa general population.

The formula for the SIR is similar to the SMR but evaluates cancer incidence instead of mortality. See formula below:

$$SIR = \sum_i W_i R_{i1} / W_i R_{i0}$$

R_{i1}= the stratum-specific rate in the AEC/DOE cohort.

R_{i0}= the stratum-specific rate in the reference population (Iowa).

W_i= stratum-specific person-years in the AEC/DOE cohort.

The NIOSH Mortality Database Program was used to maintain data files and the Life Table Analysis System (LTAS) developed by the National Institute for Occupational Safety and Health (NIOSH) was used to obtain the SIR. Several methods are available to test for statistical departures of SIRs from 1.0. We computed a chi square test with one degree of freedom. It was assumed that the observed number of cases from a particular cancer followed a random, or Poisson distribution in time. The 95% CI was used to measure the statistical variability of the SIR

For the cancer incidence analysis, person-years was accumulated: a) until the end of the study period for employees who were alive and residing in Iowa at the end of study date, b) until date of death for employees who died in Iowa during the study period, c) until date of migration from Iowa (last date known to have an Iowa residence), d) until date of last contact (usually employment termination date) for employees with unknown residence histories, or e) until cancer diagnosis date for incident cases.

In summary, person-year accumulation begins on the latest of the Iowa cancer registry inception date (January 1, 1969) or the employee's hire date. Person-year ends on the earliest of the last date of known residence in Iowa or the study closing date (December 31, 2005). Between these beginning and ending dates, subject only accrued person-time while they lived in Iowa.

<center>Relative Standardized Incidence Ratio</center>

The Relative Standardized Incidence Ratio (RSIR) is the ratio of each cause-specific site to the SIR for all cancer sites overall minus that site of interest (Breslow and Day, 1987). This method evaluates whether there is an excess or deficit of cancer cases for each specific cause relative to the overall deficit of cancers in IAAAP workers. The basic formula:

$$RSIR = SIR/((X_1 - y_1)/(X_0 - y_0))$$

SIR= observed/expected cases calculated for specific site of interest (see above).

X_1= total observed cancer in AEC/DOE cohort.

y_1= site-specific cancer in AEC/DOE cohort.

X_0= total observed cancer in Iowa reference population.

y_0= site-specific cancer in Iowa reference population.

Table 2.1 Sources of Certain Demographic Data

Data Sources	Demographic Data													
	Name	Gender	Race	SSN	Date of Birth	Vital Status	Date of Death	State of Death	Death Cert. #	State of Last Residence	Last Known Address	Job Start/End Date	Job Code	Employer Identification #
3x5" Cards	X			X									X	X	
Peoplesoft Records	X			X									X	X	
Mainframe Records	X			X									X	X	
SSA Vital Status	C			C	X	X	X			X					
SSA Earnings	C			C											X
SSA Death Master File	X			C	D	D	D	D		Z	Z				
National Death Index (NDI)	X	C		X	C	X	X	X	X						
State Death Certificates	X	X		X	X	X	X	X	X	X					
IA Cancer Registry	IA	IA		IA	IA	IA	IA	IA	IA						
IA Driver's License	IA	IA			IA										
LexisNexis	X	X	X	X	X	X						X			

NOTE: SSN= Social Security Number; X=information available; C= confirmation only; D= decedents only; Z= zip code data; IA= Iowa residents only.

Table 2.2 Missing Start and End Dates From 5,743 AEC/DOE Workers

Variable	Missing
MISSING START DATES	2,719
Have End Dates	1,373
No End Dates	1,346

Table 2.3 Missing Start Dates

Total Missing Start Dates	Have End Dates 1947-1957	Have End Dates 1958-1972	Have End Dates 1973-1991
2,719	1,359	3	11

Table 2.4 Missing Start Dates With End Dates From 1947-1957, Separated in 2-Year Increments

1947-1949	1950-1952	1953-1955	1956-1958	1990-1992
5	834	511	9	14

Figure 1 Missing data flowchart for AEC/DOE workers, alive as of December 31, 2005

AEC 5,743

Living 1,649

Missing State	**Missing DOB**	**Missing Sex**	**Missing Race**	
1,649	52	280	433	
1,649	49	280		**SSA VS**
1,649	44	280		**IA DL 05'**
999		280		**IA DL 85'**
977	44	280		**IA DL 93'**
971	44	280		**IA DL 99'**
454	34	279	431	**LN File**
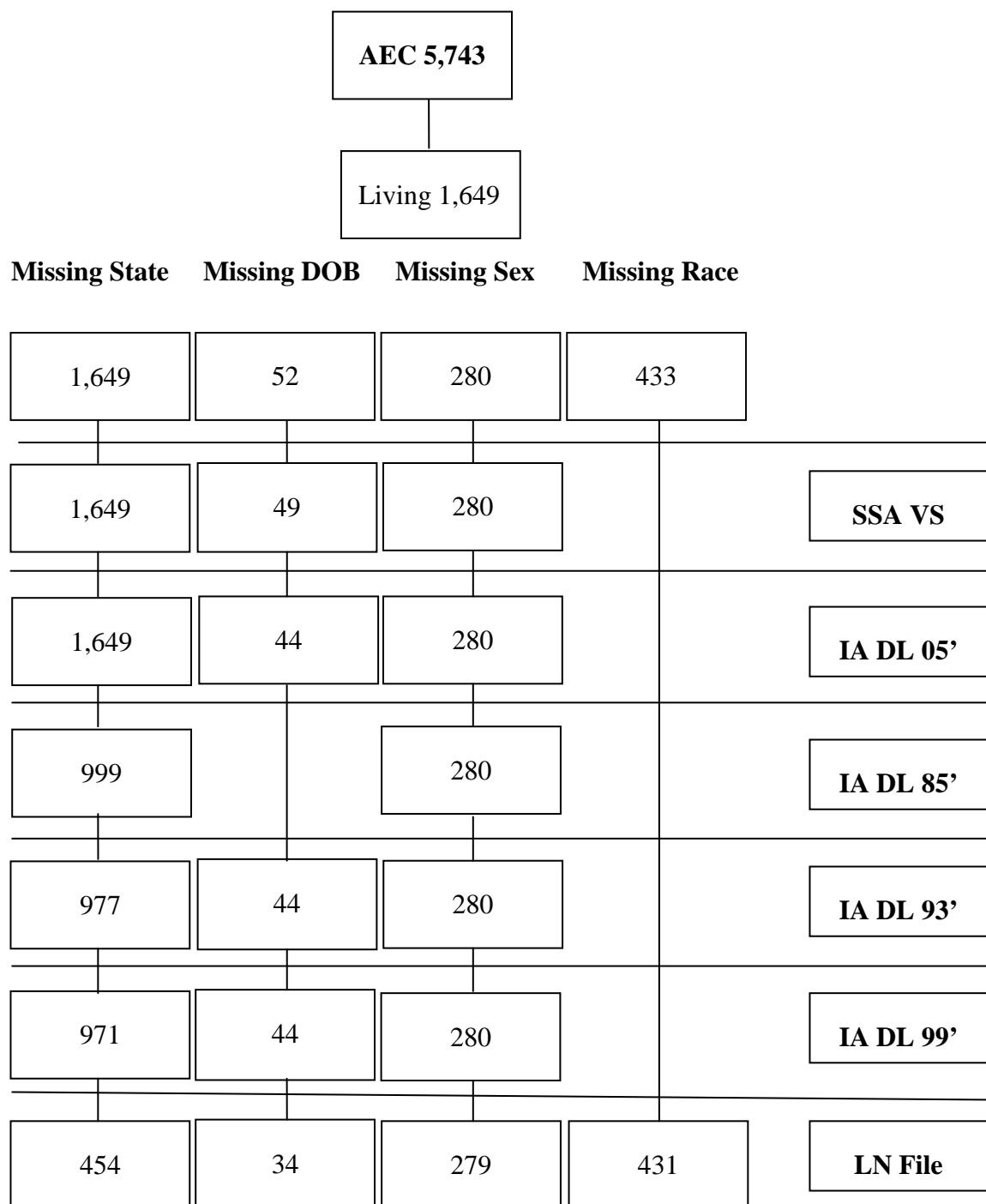
Figure 2 Missing 'state of residence' flowchart for deceased AEC/DOE workers
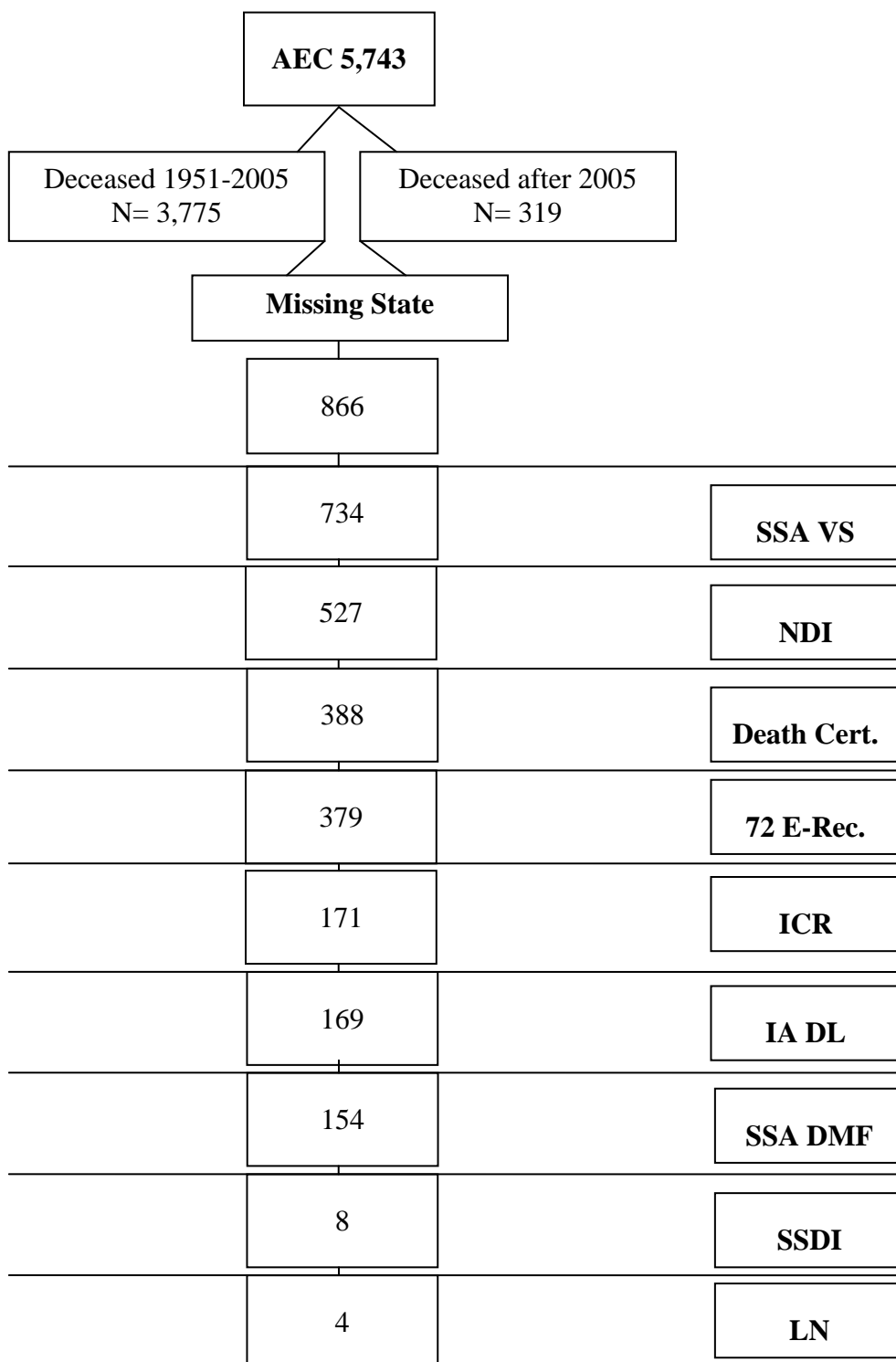
Figure 3 Missing 'date of birth' flowchart for deceased AEC/DOE workers
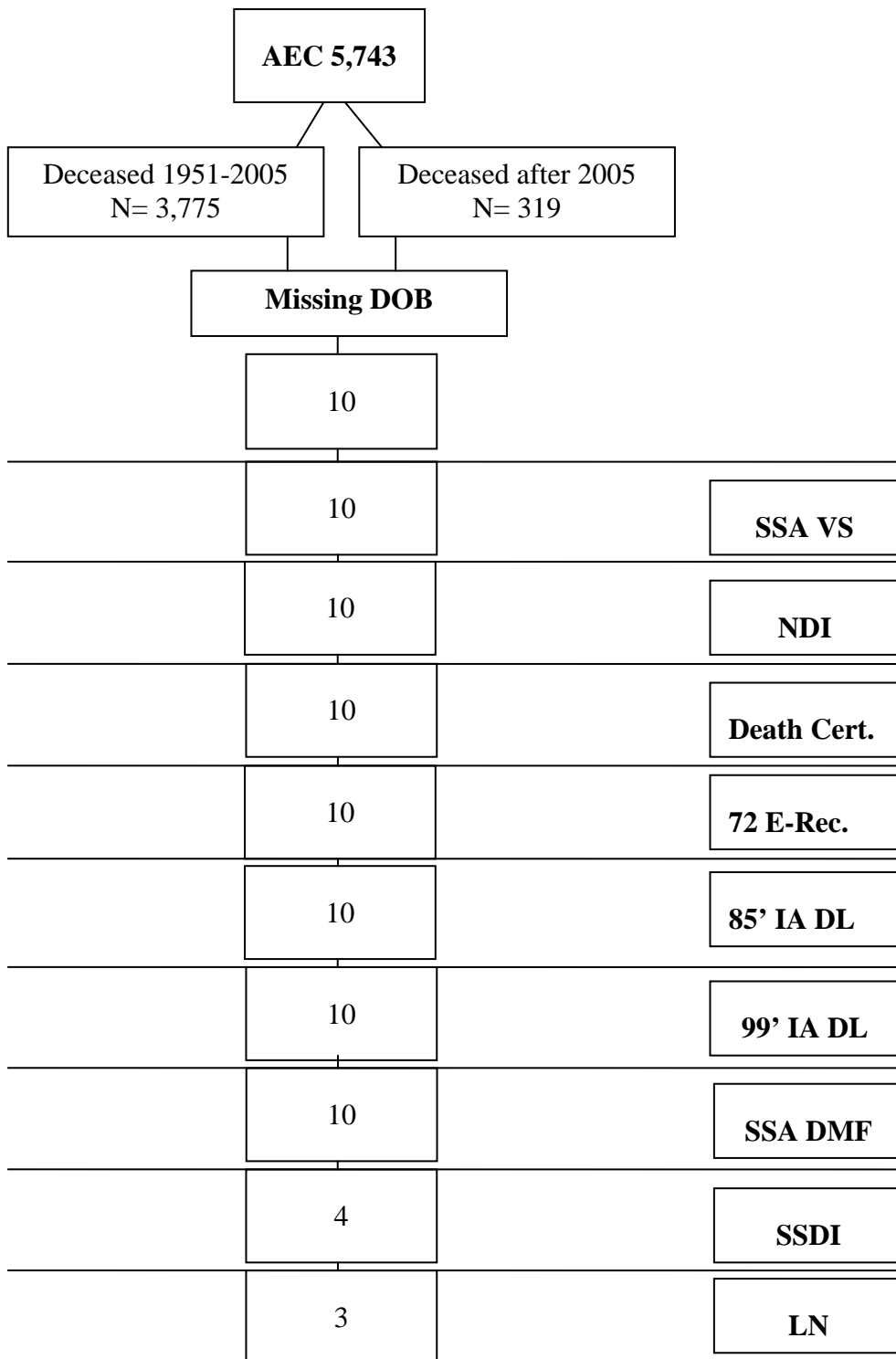
Figure 4 Missing 'gender' flowchart for deceased AEC/DDOE workers

AEC 5,743	

Deceased 1951-2005 N= 3,775	Deceased after 2005 N= 319

Missing Sex

368

368	**SSA VS**
338	**NDI**
289	**Death Cert.**
280	**72 E-Rec.**
262	**ICR**
255	**IA DL**
255	**SSA DMF**
255	**SSDI**
254	**LN**
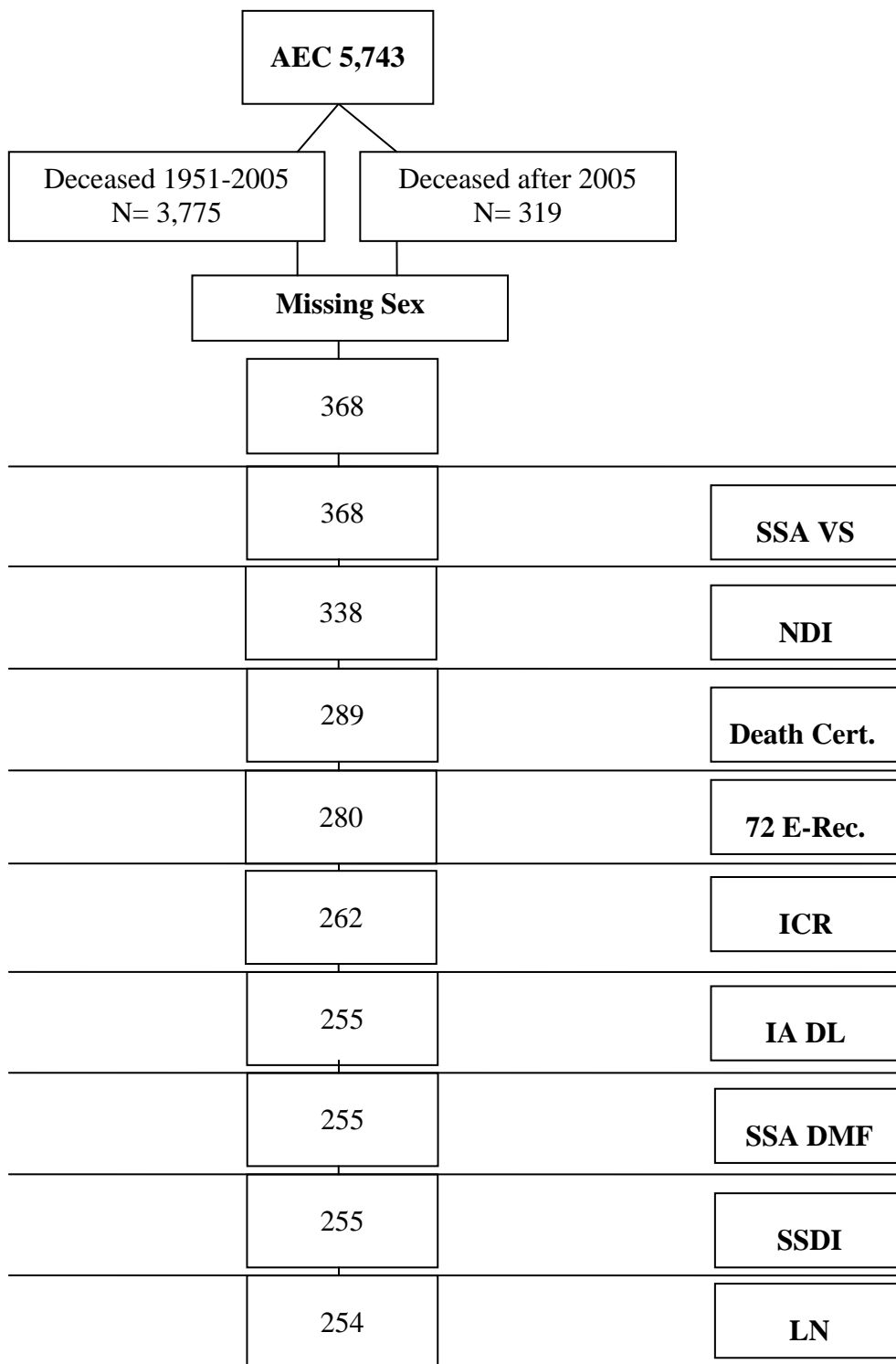
Figure 5 Missing 'race' flowchart for deceased AEC/DOE workers
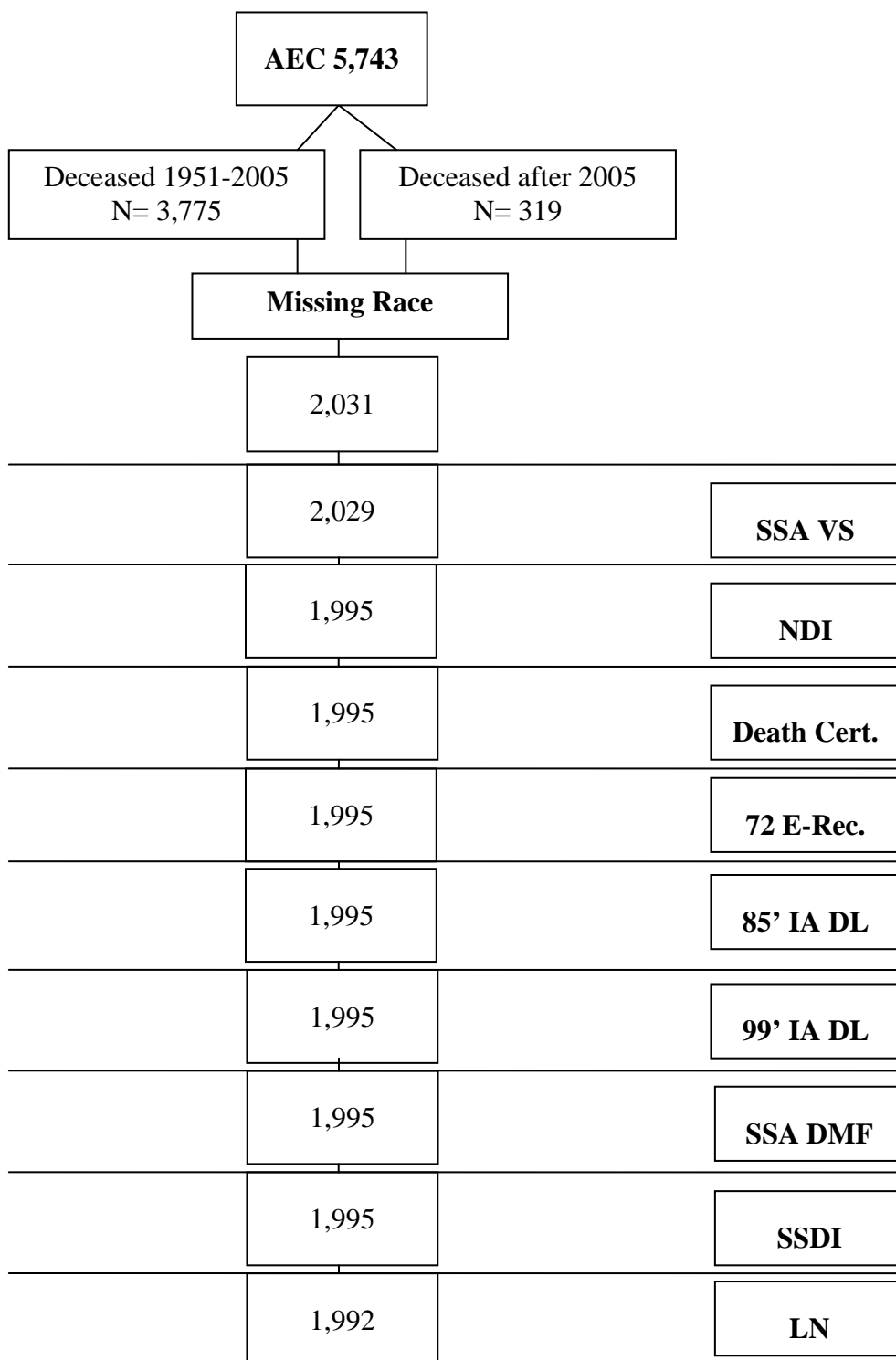
Figure 6 Missing 'date of death' flowchart for deceased AEC/DOE workers
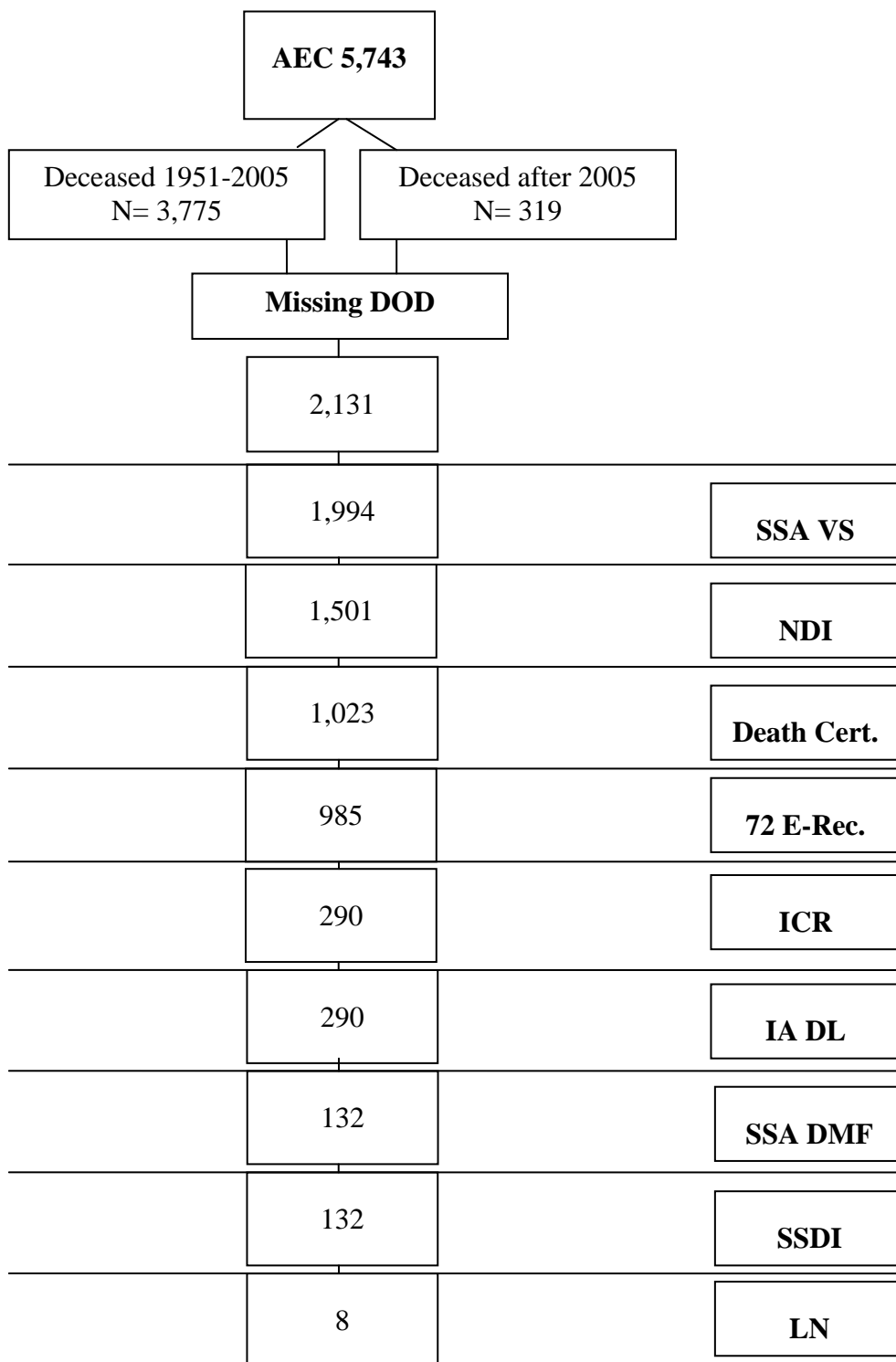
Figure 7 Decision tree for missing start and end dates
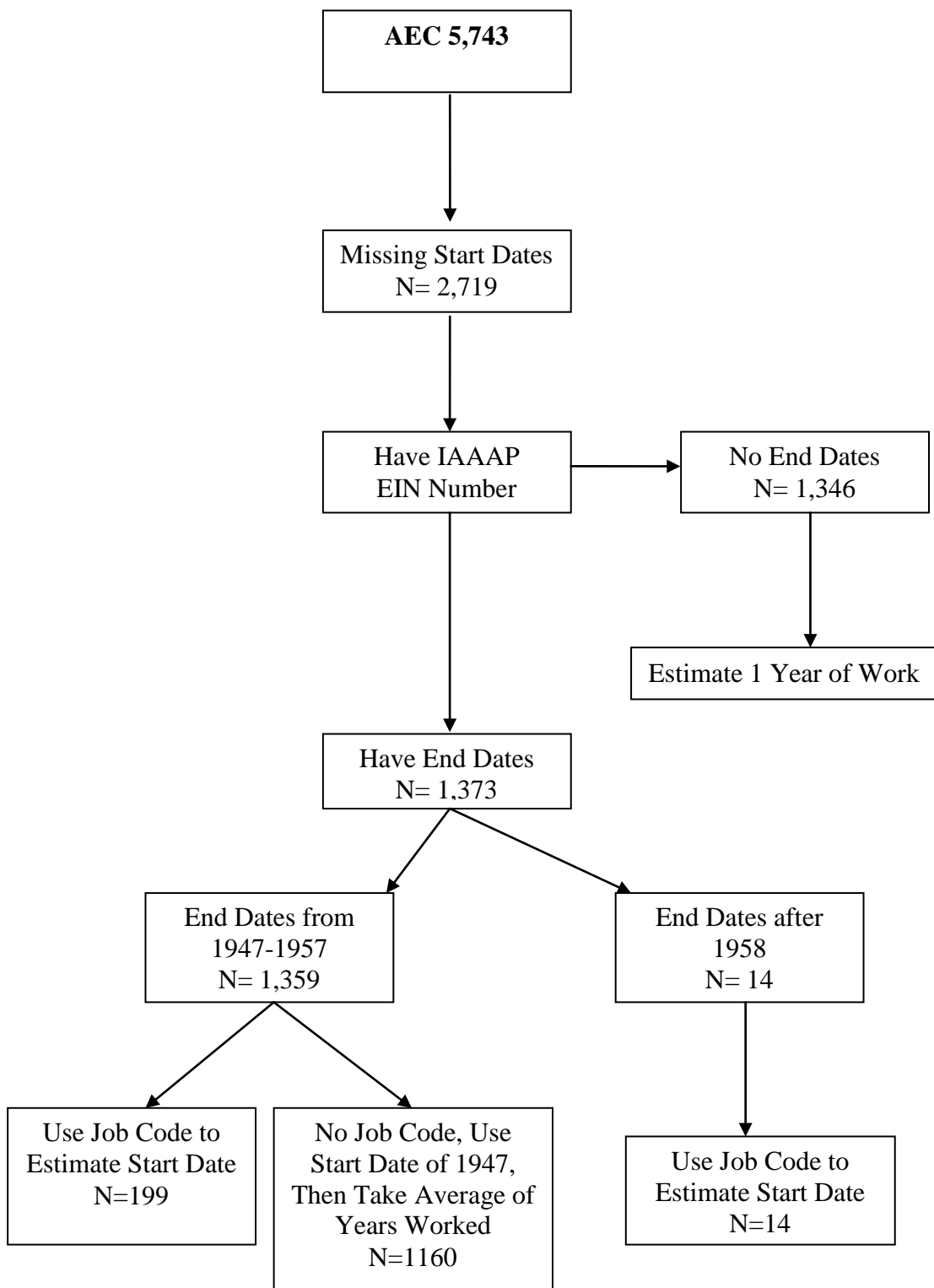
CHAPTER THREE: RESULTS

Results of the cancer incidence and mortality study of former AEC/DOE workers are presented below.   The cancer incidence portion covers the years 1969-2005 (excluding 1972) while the mortality study includes the early years of production from 1948-2005.

Cancer Incidence

A total of 3,889 AEC/DOE workers met the criteria for inclusion into the cancer incidence portion of the study (Table 3.1). There were 3,285 men and 604 women. At the end of the study, December 31, 2005, there were 749 cancers diagnosed in the state of Iowa. The average age at start date at IAAAP was 32 for men and 30 for women (Table 3.2). The median age at the end of follow-up was 75 for men and 76 for women. There were a total of 76,889 person-years of follow-up for men and 15,725 person-years follow-up for women. At the end of the study December 31, 2005 there were 3,178 deceased, 668 alive and 43 lost to follow-up.

Proportional Incidence Ratios

A proportional incidence ratio (PIR) analysis was performed, stratified by age, non-retired (age 0-64) and retired (65 +), and by sex. There were 487 males in the 0-64 age male category, see Table 3.3. PIR analyses showed non-significant decreases in cancers of the oral cavity/pharynx, larynx, brain, bladder, kidney, skin, Hodgkin lymphoma, non-Hodgkin lymphoma and other cancers. These results were based on a small number of cases, generally fewer than 10. A significant deficit was observed for prostate cancer (PIR 0.64, 95% CI 0.41-0.99). Excesses were noted for certain cancers, although these were also based on very few cases. Non-significant PIRs over one were observed for cancers of the lip (4 cases), esophagus (4 cases), stomach (4 cases), colon (21 cases), CML (2 cases) and leukemia (excluding CLL) (2 cases). Statistically

significant excesses were observed for cancers of the rectum (n=14, PIR 1.78, 95% CI 1.08-2.94), pancreas (n=8, PIR 1.99, 95% CI 1.01-3.91), male breast (n=2, PIR 6.84, 95% CI 1.72-27.1), lung (n=45, PIR 1.44, 95% CI 1.12, 1.85), and CLL (n=6, PIR 2.51, 95% CI 1.14-5.51).

There were 2,798 males in the retired 65+ category, see Table 3.4. PIR analyses showed non-significant decreases in cancers of the thyroid, stomach, colon, bladder, prostate, non-Hodgkin lymphoma, AML, CLL and multiple myeloma. Non-significant PIRs over one were observed for cancers of the lip (5 cases), brain (5 cases), esophagus (9 cases), larynx (7 cases), rectum (22 cases), liver/gallbladder (6 cases), pancreas (12 cases), kidney (13 cases), melanoma (10 cases), other leukemia (4 cases), CML (3 cases) and other cancers (12 cases). Significant excesses were observed for cancers of the oral cavity and pharynx (n=8, PIR 2.60 95% CI 1.31-5.17), lung (n=108, PIR 1.27, 95% CI 1.07-1.50), mesothelioma (n=4, PIR 4.0, 95% CI 1.50-10.6) and testes (n=3, PIR 6.31, 95% CI 2.04-19.5).

There were 81 females in the 0-64 age category, see Table 3.5. PIR analyses demonstrated excesses for certain cancers, although these were based on very few cases. Non-significant PIRs over one were observed for cancers of the colon (5 cases), rectum (2 cases), lung (4 cases) and bladder (2 cases), breast (15 cases), cervix (3 cases) and ovary (2 cases). A significant increase in cancer incidence was observed for cancer of the pancreas (n=2, PIR 4.10, 95% CI 1.06-15.78).

There were 523 females in the retired 65+ category, see Table 3.6. PIR analyses showed non-significant decreases in cancers of the colon, rectum, pancreas, and breast. Non-significant PIRs over one were observed for cancers of the lung (11 cases), kidney (2 cases), uterus (6 cases), ovary (3 cases), non-Hodgkin lymphoma (4 cases), CLL (2 cases) and other cancers (2 cases). A significant increase was observed in CML (PIR 6.79, 95% CI 1.73-26.6) and cervical cancer (PIR 7.29, 95% CI 3.13-16.9), although this was based on only 2 and 5 cases respectively.

Standardized Incidence Ratios

Standardized incidence ratios (SIRs) were calculated using the same sub-set of employees from the PIR analyses. There were 637 primary cancers diagnosed for men and 112 for women. Former IAAAP employees had significantly lower incidence of cancer overall compared with the general population in Iowa. All site SIR analyses for men and women were (SIR 0.63, 95% CI 0.58-0.68) and (SIR 0.81, 95% CI 0.67-0.98), respectively. For men, there were also significant deficits (see Table 3.7) in cancers of the stomach (n= 9, SIR 0.40, 95% CI 0.18-0.76), colon (n=64, SIR 0.60, 95% CI 0.46-0.77), lung (n=153, SIR 0.73, 95% CI 0.62-0.85), bladder (n=42, SIR 0.56, 95% CI 0.40-0.74), kidney (n=17, SIR 0.58, 95% CI 0.58-0.68), prostate (n=133, SIR 0.54, 95% CI 0.45-0.64), other cancers (n=15, SIR 0.57, 95% CI 0.32-0.93), AML (n=2, SIR 0.26, 95% CI 0.03-0.98) and non-Hodgkin lymphoma (n=21, SIR 0.62, 95% CI 0.38-0.94).

Other SIR analyses for men showed non-significant deficits in cancers of the oral cavity/pharynx, lip, brain, thyroid, rectum, liver/gallbladder, pancreas, melanoma, multiple myeloma, all leukemia and CLL. Non-significant excesses were noted for cancers of the esophagus, mesothelioma, testis, and CML.

SIR analyses for women (see Table 3.8) showed non-significant deficits in cancers of the brain, thyroid, colon, rectum, bladder, kidney, melanoma, breast, uterus, ovary, non-Hodgkin lymphoma and other cancers. Non-significant excesses were noted in cancers of the lung (10 cases), pancreas (4 cases), liver/gallbladder (2 cases), cervix (8 cases), all leukemia (5 cases), CLL (2 cases), and CML (2 cases).

Relative Standardized Incidence Ratios

Relative SIRs for selected cancers among male and female IAAAP employees are presented in Tables 3.9 and 3.10 respectively. A significant relative excess of lung cancer was observed for men (RSIR=1.22, 95% CI 1.01-1.47). Among women, a

significant relative excess of cervical cancer was observed (RSIR=3.49, 95% CI 1.47-7.13).

Mortality

A total of 5,743 (4,923 men and 820 women) AEC/DOE workers met the criteria for inclusion into the mortality portion of the study (Table 3.11). At the end of the study December 31, 2005, 64% of the cohort was deceased (3,222 men and 422 women). For men, the average age at start date was 34 years (Table 3.12) and average year of hire was 1950. Women were on average 30 years old at start date and had an average year of hire of 1951. The median age at the end of follow-up is 75 for men and 77 for women. On average, both men and women worked only 2 years at IAAAP. There were a total of 138,862 person-years of follow-up for men and 26,001 person-years follow-up for women.

Standardized Mortality Ratios for AEC/DOE Workers
Compared to the U.S. Population

For men, overall mortality was significantly less than expected (SMR=0.94, 95% CI 0.91-0.98), see Table 3.13. Cause-specific mortality analyses demonstrated significant deficits in deaths due to stomach cancer (SMR 0.41, 95% CI 0.21-0.72), heart disease (SMR 0.88, 95% CI 0.83-0.93), ischemic heart disease (SMR 0.89, 95% CI 0.84-0.94), diseases of the genitourinary system (SMR 0.65, 95% CI 0.45-0.90) and cirrhosis of the liver (SMR 0.60, 95% CI 0.42-0.84). Significant excesses in mortality were observed for all respiratory cancers (SMR 1.27, 95% CI 1.13-1.41), lung cancer (SMR 1.29, 95% CI 1.15-1.44), diseases of the respiratory system (SMR 1.16, 95% CI 1.04-1.29) and COPD (SMR 1.34, 95% CI 1.15-1.54).

For women (Table 3.14), overall mortality was significantly greater (SMR 1.15, 95% CI 1.04-1.27). Other cause-specific significant excesses include: all cancers (SMR

1.32, 95% CI 1.10-1.58), lung cancer (SMR 1.97, 95% CI 1.37-2.75), and COPD (SMR 2.03, 95% CI 1.31-3.00). No significant deficits were identified.

Standardized Mortality Ratios for AEC/DOE Workers

Compared to the Iowa Population

Standardized Mortality Ratios (SMRs) were calculated using the Iowa population as reference. For men (Table 3.15), significant deficits were observed for all stomach cancer (SMR=0.50, 95% CI 0.26-0.87) and ischemic heart disease (SMR 0.93, 95% CI 0.87-0.99). There were significant excesses for all cancers (SMR 1.09, 95% CI 1.02-1.17), lung cancer (SMR 1.38, 95% CI 1.24-1.54), mesothelioma (SMR 6.20, 95% CI 1.28-18.13), diseases of the respiratory system (SMR 1.15, 95% CI 1.03-1.46), COPD (SMR 1.27, 95% CI 1.10-1.46), and asbestosis (SMR 9.28, 95% CI 1.12-33.5). Elevated SMRs for mesothelioma and asbestosis were based on very few cases, n=3 and n=2, respectively.

For women (Table 3.16) excesses were observed for all cancers (SMR 1.41, 95% CI 1.17-1.69), lung cancer (SMR 2.47, 95% CI 1.72-3.44), ischemic heart disease (SMR 1.32, 95% CI 1.09-1.58), respiratory diseases (SMR 1.59, 95% CI 1.14-2.16) and COPD (SMR 2.47, 95% CI 1.60-3.65). There were no significant deficits.

Summary information on the different statistical analyses is presented in Tables 3.17 and 3.18.

Table 3.1 Distribution of Workers in the Incidence Cohort by Gender and Follow-Up
Status

AEC/DOE Incidence Cohort	Men	%	Women	%
Total	3,285	84.4	604	15.5
Age *				
<49	29	0.9	8	1.3
50-59	178	5.4	42	7.0
60-69	741	22.6	99	16.4
70-79	1,314	40.0	241	39.9
80-89	866	26.4	161	26.7
90-99	151	5.0	52	8.6
>100	6	0.2	1	0.2
Race				
White	2,112	64.3	426	70.5
Nonwhite	1,128	34.3	19	3.1
Unknown race	45	1.4	159	26.3
Vital Status				
Deceased	2,762	84.1	416	68.9
Alive	492	15.0	176	29.1
Lost to follow-up	31	0.9	12	2.0
Start date of employment				
<1946	421	12.8	15	2.5
1947-1956	2,511	76.4	508	84.1
1957-1966	311	9.5	59	9.8
1967-1975	42	1.3	22	3.6
End date of employment				
1947-1956	1,651	50.3	356	58.9
1957-1966	491	14.9	53	8.8
1967-1976	769	23.4	146	24.2
1977-1986	202	6.1	28	4.6
1987-1996	143	4.4	15	2.5
1997-2005	29	0.9	6	1.0
Years worked at IAAAP				
< 1	84	2.6	15	2.5
1-< 5	1,647	50.1	350	57.9
5- < 10	529	16.1	120	19.9
10- < 15	198	6.0	27	4.5
15- < 20	213	6.5	18	3.0
20 +	614	18.7	74	12.3
Incident Cancers	749		122	
Person-Years	76,889		15,725	

Note: *Age at end of follow-up December 31, 2005.

Table 3.2 Descriptive Statistics of Workers in the Incidence Cohort by Gender

AEC/DOE Incidence Cohort	Male		Female	
	Mean	SD	Mean	SD
Year of birth	1918	11	1921	12
Year of hire	1950	5	1951	5
Age at start date (years)	32	11	30	11
Duration of employment (years)	2	1	2	1
Length of follow-up (years)	24	14	26	13

Table 3.3 Proportional Incidence Ratios (PIRs) and 95% Confidence Intervals (CIs) for AEC/DOE Workers vs. the State of Iowa for Males Ages 0-64, 1969-2005, Excluding 1972

Cancer Site	Number of Cancer Cases		PIR	95% CI
	AEC/DOE	IA		
Oral cavity/Pharynx	2	1307	0.71	(0.18, 2.82)
Lip	4	899	2.07	(0.78, 5.45)
Brain	3	2276	0.61	(0.20, 1.88)
Esophagus	4	1176	1.58	(0.60, 4.17)
Stomach	4	1515	1.22	(0.47, 3.23)
Colon	21	6657	1.46	(0.98, 2.19)
Rectum	14	3658	**1.78**	(1.08, 2.94)
Pancreas	8	1869	**1.99**	(1.01, 3.92)
Lung and Bronchus	45	14549	**1.44**	(1.12, 1.85)
Larynx	3	1932	0.72	(0.24, 2.22)
Urinary Bladder	8	4623	0.80	(0.40, 1.58)
Kidney/Renal Pelvis	4	3228	0.58	(0.22, 1.52)
Melanoma of the Skin	4	4305	0.43	(0.16, 1.14)
Male Breast	2	136	**6.84**	(1.72, 27.1)
Prostate	18	13044	**0.64**	(0.41, 0.99)
Hodgkin Lymphoma	2	1238	0.75	(0.19, 2.98)
Non-Hodgkin Lymphoma	6	3839	0.73	(0.33, 1.60)
Leukemia, except CLL	2	653	1.42	(0.36, 5.65)
CLL	6	1112	**2.51**	(1.14, 5.51)
CML	2	404	2.30	(0.58, 9.10)
Other Cancers	3	1753	0.80	(0.26, 2.44)
All Sites	173	80454	Reference	

Table 3.4 Proportional Incidence Ratios (PIRs) and 95% Confidence Intervals (CIs) for AEC/DOE Workers vs. the State of Iowa for Males Ages 65+, 1969-2005, Excluding 1972

Cancer Site	Number of Cancer Cases		PIR	95% CI
	AEC/DOE	IA		
Oral cavity/Pharynx	8	1067	**2.60**	(1.31, 5.17)
Lip	5	1682	1.03	(0.43, 2.47)
Brain	5	1438	1.21	(0.50, 2.88)
Thyroid	1	452	0.77	(0.11, 5.44)
Esophagus	9	1934	1.61	(0.85, 3.08)
Stomach	5	3335	0.53	(0.22, 1.24)
Colon	43	17330	0.86	(0.65, 1.14)
Rectum	22	6730	1.13	(0.75, 1.71)
Liver and Gallbladder	6	1987	1.04	(0.47, 2.32)
Pancreas	12	3959	1.05	(0.60, 1.83)
Lung and Bronchus	108	29557	**1.27**	(1.07, 1.50)
Larynx	7	2098	1.16	(0.56, 2.41)
Pleura (Mesothelioma)	4	348	**4.0**	(1.50, 10.6)
Urinary Bladder	34	12744	0.93	(0.67, 1.28)
Kidney/Renal Pelvis	13	4388	1.04	(0.61, 1.78)
Melanoma of the Skin	10	3350	1.04	(0.56, 1.91)
Prostate	115	46761	0.85	(0.73, 1.00)
Testes	3	165	**6.31**	(2.04, 19.5)
Non-Hodgkin Lymphoma	12	5258	0.79	(0.45, 1.38)
Leukemia, except CLL	4	991	1.40	(0.53, 3.71)
AML	2	1247	0.56	(0.14, 2.22)
CML	3	721	1.44	(0.47, 4.46)
CLL	7	2732	0.89	(0.42, 1.85)
Multiple Myeloma	6	2138	0.97	(0.44, 2.16)
Other Cancers	12	4087	1.02	(0.58, 1.78)
All Sites	464	160,997	Reference	

Table 3.5 Proportional Incidence Ratios (PIRs) and 95% Confidence Intervals (CIs) for AEC/DOE Workers vs. the State of Iowa for Females Ages 0-64, 1969-2005, Excluding 1972

Cancer Site	Number of Cancer Cases		PIR	95% CI
	AEC/DOE	IA		
Colon	5	6214	1.86	(0.82, 4.21)
Rectum	2	2621	1.76	(0.45, 6.79)
Pancreas	2	1127	**4.10**	(1.06, 15.78)
Lung and Bronchus	4	2823	1.18	(0.47, 2.98)
Urinary Bladder	2	1341	3.44	(0.89, 13.26)
Female Breast	15	30986	1.12	(0.75, 1.66)
Cervix	3	3640	1.90	(0.64, 5.64)
Ovary	2	4304	1.07	(0.28, 4.13)
All Sites	39	89912	Reference	

Table 3.6 Proportional Incidence Ratios (PIRs) and 95% Confidence Intervals (CIs) for AEC/DOE Workers vs. the State of Iowa for Females Ages 65+, 1969-2005, Excluding 1972

Cancer Site	Number of Cancer Cases		PIR	95% CI
	AEC/DOE	IA		
Colon	7	23013	0.59	(0.29, 1.19)
Rectum	3	6082	0.95	(0.31, 2.88)
Pancreas	2	4670	0.82	(0.21, 3.23)
Lung and Bronchus	11	14879	1.42	(0.83, 2.46)
Kidney/Renal Pelvis	2	3189	1.21	(0.31, 4.74)
Female Breast	17	35412	0.93	(0.61, 1.40)
Cervix	5	1323	**7.29**	(3.13, 16.9)
Uterus	6	8040	1.44	(0.67, 3.10)
Ovary	3	4755	1.22	(0.40, 3.69)
Non-Hodgkin Lymphoma	4	6046	1.28	(0.49, 3.31)
CML	2	568	**6.79**	(1.73, 26.6)
CLL	2	2180	1.77	(0.45, 6.94)
Other Cancers	2	4913	3.07	(0.20, 3.08)
All Sites	73	140753	Reference	

Table 3.7 Standardized Incidence Ratios (SIRs) for Various Cancers Among Male
Employees with IAAAP Workplace Exposures, 1969-2005, Excluding 1972

Cancer Site	Cancer Cases		SIR	95% CI
	AEC/DOE Observed	IA Expected		
All Cancers	637	1018.8	**0.63**	(0.58, 0.68)
Oral cavity/pharynx	28	39.5	0.71	(0.47, 1.03)
Lip	9	13.5	0.67	(0.31, 1.28)
Brain	8	12.9	0.62	(0.27, 1.22)
Thyroid	2	3.6	0.55	(0.07, 1.98)
Esophagus	13	12.3	1.06	(0.56, 1.81)
Stomach	9	22.3	**0.40**	(0.18, 0.76)
Colon	64	106.2	**0.60**	(0.46, 0.77)
Rectum	36	47.5	0.76	(0.53, 1.04)
Liver and Gallbladder	7	11.8	0.59	(0.24, 1.22)
Pancreas	20	25	0.77	(0.47, 1.19)
Lung and Bronchus	153	211	**0.72**	(0.62, 0.85)
Mesothelioma	4	2	1.93	(0.53, 4.95)
Urinary Bladder	42	75	**0.56**	(0.40, 0.74)
Kidney/Renal Pelvis	17	29	**0.58**	(0.34, 0.93)
Melanoma of the Skin	14	21	0.66	(0.36, 1.10)
Prostate	133	247	**0.54**	(0.45, 0.64)
Testis	3	3	1.14	(0.23, 3.32)
Non-Hodgkin Lymphoma	21	34	**0.62**	(0.38, 0.94)
Leukemia	25	35	0.72	(0.46, 1.06)
CLL	13	16	0.78	(0.41, 1.33)
CML	5	4	1.15	(0.37, 2.69)
AML	2	7	**0.26**	(0.03, 0.96)
Other Leukemia	5	6	0.79	(0.26, 1.83)
Multiple Myeloma	7	13	0.54	(0.22, 1.11)
Other Cancers	15	26	**0.57**	(0.32, 0.93)

Table 3.8 Standardized Incidence Ratios (SIRs) for Various Cancers Among Female Employees with IAAAP Workplace Exposures, 1969-2005, Excluding 1972

Cancer Site	Number of Cancer Cases		SIR	95% CI
	AEC/DOE observed	IA Expected		
All Cancers	112	137.7	**0.81**	(0.67, 0.98)
Brain	1	1.7	0.59	(0.02, 3.31)
Thyroid	1	1.4	0.70	(0.02, 3.90)
Colon	12	17.9	0.67	(0.35, 1.17)
Rectum	5	5.4	0.93	(0.30, 2.16)
Liver and Gallbladder	2	1.9	1.08	(0.13, 3.90)
Pancreas	4	3.4	1.19	(0.32, 3.05)
Lung and Bronchus	15	13.6	1.10	(0.61, 1.81)
Urinary Bladder	2	3.3	0.61	(0.07, 2.19)
Kidney/Renal Pelvis	2	2.8	0.71	(0.09, 2.57)
Melanoma of the Skin	2	2.7	0.65	(0.35, 1.08)
Breast	32	39.6	0.81	(0.55, 1.14)
Uterus	8	10.6	0.76	(0.33, 1.49)
Cervix	8	4.7	1.71	(0.74, 3.37)
Ovary	5	6.0	0.84	(0.27, 1.95)
Non-Hodgkin Lymphoma	4	5.14	0.78	(0.21, 1.99)
All Leukemia	5	3.6	1.38	(0.45, 3.23)
CLL	2	1.6	1.22	(0.15, 4.41)
CML	2	0.47	4.25	(0.51, 15.3)
Other Leukemia	1	0.6	1.67	(0.04, 9.33)
Other Cancers	10	17.9	0.56	(0.27, 1.03)

Table 3.9 Relative Standardized Incidence Ratios (RSIRs) for Selected Cancers Among Male IAAAP Employees

Cancer Site	Obs (N)	RSIR	95% CI
Oral cavity and pharynx	28	1.15	(0.76, 1.67)
Lip	9	1.09	(0.50, 2.07)
Esophagus	13	1.72	(0.91, 2.96)
Stomach	9	0.64	(0.29, 1.23)
Colon	64	0.97	(0.74, 1.26)
Rectum	36	1.22	(0.85, 1.71)
Pancreas	20	1.24	(0.75, 1.94)
Larynx	10	0.80	(0.38, 1.47)
Lung	153	**1.22**	(1.01, 1.47)
Bladder	42	0.89	(0.64, 1.22)
Kidney	17	0.92	(0.53, 1.48)
Prostate	133	0.83	(0.68, 1.01)
Brain	8	0.98	(0.42, 1.93)
Non-Hodgkin Lymphoma	21	0.99	(0.61, 1.53)
Leukemia	25	1.16	(0.75, 1.73)
CLL	13	1.24	(0.64, 1.22)

Table 3.10 Relative Standardized Incidence Ratios (RSIRs) for Selected Cancers Among Female IAAAP Employees

Cancer Site	Obs (N)	RSIR	95% CI
Colon	12	0.80	(0.40, 1.46)
Rectum	5	1.14	(0.36, 2.74)
Lung	15	1.34	(0.74, 2.39)
Breast	32	0.97	(0.62, 1.48)
Cervix	8	**3.49**	(1.47, 7.13)
Ovary	5	1.02	(0.32, 2.45)

Table 3.11 Distribution of Workers in the Mortality Cohort by Gender and Follow-Up Status (Follow-Up Through December 31, 2005)

AEC/DOE Mortality Cohort	Men	%	Women	%
Total	4,923	85.7	820	14.3
Age				
<49	143	2.9	18	2.2
50-59	413	8.4	66	8.0
60-69	1,110	22.5	124	15.1
70-79	1,829	37.2	341	41.6
80-89	1,168	23.7	208	25.4
90-99	216	4.4	57	7.0
>100	14	0.3	2	0.2
Unknown Age	30	0.6	4	0.4
Race				
White	2,647	53.8	559	68.2
Nonwhite	54	1.1	28	3.4
Unknown race	2,222	45.1	233	28.4
Vital Status				
Deceased	3,993	81.1	510	62.2
Alive	837	17.0	289	35.2
Lost to follow-up	93	1.9	21	2.6
Start date of employment				
<1946	549	11.2	22	2.7
1947-1956	3,890	79.0	693	84.5
1957-1966	432	8.8	81	9.9
1967-1975	52	1.1	24	2.9
End date of employment				
1947-1956	2,829	57.5	520	63.4
1957-1966	766	15.6	82	10.0
1967-1976	937	19.0	169	20.6
1977-1986	206	4.2	28	3.4
1987-1996	152	3.1	15	1.8
1997-2005	33	0.7	6	0.7
Years worked at IAAAP				
< 1	154	3.1	25	3.0
1-< 5	2,746	55.8	506	61.7
5- < 10	768	15.6	154	18.8
10- < 15	285	5.8	38	4.6
15- < 20	287	5.8	22	2.7
20 +	683	13.9	75	9.1
Total Deaths	3,222		422	
Person-Years	138,862		26,901	

Table 3.12 Descriptive Statistics of Workers in the Mortality Cohort by Gender

AEC/DOE Mortality Cohort	Male		Female	
	Mean	SD	Mean	SD
Year of birth	1917	14	1921	13
Year of hire	1950	4.8	1951	5.1
Age at start date (years)	34	13	30	12
Duration of employment (years)	2.0	1.3	1.9	1.1
Length of follow-up (years)	29.0	12.1	33.6	10.0

Table 3.13 Standardized Mortality Ratios (SMRs) for Male IAAAP Workers Compared
to the U.S. Population, 1951-2005

Mortality	Number of Cases		SMR	95% CI
	AEC/DOE observed	U.S. expected		
All Cause	3,222	3,409	**0.94**	(0.91, 0.98)
All Cancers	805	772.2	1.04	(0.97, 1.12)
Oral Cavity and Pharynx	18	18.2	0.99	(0.59, 1.57)
Esophagus	21	19.1	1.10	(0.23, 0.89)
Stomach	12	29.3	**0.41**	(0.21, 0.72)
Colon	69	72.9	0.95	(0.74, 1.20)
Rectum	18	18.0	1.00	(0.59, 1.58)
Liver and Gallbladder	20	19.1	1.05	(0.64, 1.62)
Pancreas	33	39.6	0.83	(0.57, 1.17)
All Respiratory	339	268.0	**1.27**	(1.13, 1.41)
Larynx	7	9.6	0.73	(0.29, 1.51)
Pleura	2	0.8	2.45	(0.30, 8.86)
Lung and Bronchus	330	255.8	**1.29**	(1.15, 1.44)
Mesothelioma	3	0.71	4.25	(0.88, 12.43)
Urinary Cancers	51	43.5	1.17	(0.87, 1.54)
Bladder	31	25.1	1.23	(0.84, 1.75)
Kidney and Renal Pelvis	20	18.3	1.09	(0.67, 1.69)
Melanoma of the Skin	9	9.7	0.93	(0.43, 1.77)
Prostate	70	79.9	0.88	(0.68, 1.11)
Brain	17	16	1.02	(0.59, 1.64)
Lymphatic/Hematopoietic	74	70.8	1.04	(0.82, 1.31)
Leukemia	30	29.2	1.03	(0.69, 1.47)
Hodgkin's Lymphoma	5	3.8	1.31	(0.43, 3.06)
Non-Hodgkin's Lymphoma	24	26.0	0.92	(0.59, 1.37)
Multiple Myeloma	15	11.8	1.27	(0.71, 2.09)
Heart Disease	1,209	1,376.1	**0.88**	(0.83, 0.93)

'Table 3.13 continued'

Mortality	AEC/DOE Observed	IA Expected	SMR	95% CI
Ischemic Heart Disease	1,049	1,180.5	**0.89**	(0.84, 0.94)
Cerebrovascular disease	230	247.4	0.93	(0.81, 1.06)
Diabetes Mellitus	54	58.8	0.92	(0.69, 1.20)
Diseases Digestive System	110	131.8	0.83	(0.69, 1.01)
Cirrhosis	34	56.6	**0.60**	(0.42, 0.84)
Diseases of Genitor-Urinary System	35	53.9	**0.65**	(0.45, 0.90)
Nervous System Disorders	57	46.6	1.22	(0.93, 1.59)
Diseases Respiratory System	336	289.0	**1.16**	(1.04, 1.29)
Pneumonia	104	98.4	1.06	(0.86, 1.28)
COPD	190	1.41	**1.34**	(1.15, 1.54)
Asbestosis	2	0.66	3.01	(0.37, 10.89)
Injury	35	41.6	0.84	(0.59, 1.17)
Suicide	32	42.5	0.75	(0.52, 1.06)

Table 3.14 Standardized Mortality Ratios (SMRs) for Female IAAAP Workers
Compared to the U.S. Population, 1951-2005

Mortality	Number of Cases		SMR	95% CI
	AEC/DOE Observed	U.S. Expected		
All Cause	422	367	**1.15**	(1.04, 1.27)
All Cancers	122	92.3	**1.32**	(1.10, 1.58)
Esophagus	1	0.89	1.13	(0.03, 6.31)
Stomach	2	2.27	0.88	(0.11, 3.18)
Colon	11	9.88	1.11	(0.56, 1.99)
Liver and Gallbladder	5	2.40	0.68	(0.68, 4.86)
Pancreas	6	4.81	1.25	(0.46, 2.71)
Lung and Bronchus	35	17.7	**1.97**	(1.37, 2.75)
Kidney and Renal Pelvis	3	1.54	1.95	(0.40, 5.70)
Breast	20	17.4	1.15	(0.70, 1.77)
Ovary	6	5.82	1.03	(0.38, 2.24)
Uterus	1	2.61	0.38	(0.01, 2.13)
Cervix	3	2.24	1.34	(0.28, 3.91)
Brain	4	2.08	1.93	(0.53, 4.93)
Lymphatic/Hematopoietic	9	8.3	1.08	(0.50, 2.60)
Non-Hodgkin Lymphoma	3	3.40	0.88	(0.18, 2.58)
Leukemia	4	3.03	1.32	(0.50, 2.60)
Multiple Myeloma	2	1.50	1.34	(0.16, 4.84)
Diseases of Digestive System	17	14.7	1.16	(0.67, 1.85)
Diabetes Mellitus	8	9.50	0.84	(0.36, 1.66)
Ischemic Heart Disease	119	99.8	1.19	(0.99, 1.43)
Respiratory Disease	24	30	0.81	(0.52, 1.21)
COPD	25	12.31	**2.03**	(1.31, 3.00)
Cerebrovascular disease	44	34.3	1.28	(0.93, 1.72)
Injury	7	8.08	0.87	(0.35, 1.78)

Table 3.15 Standardized Mortality Ratios (SMRs) for Male IAAAP Workers Compared to the Iowa Population, 1951-2005

Mortality	Number of Cases		SMR	95% CI
	AEC/DOE Observed	IA Expected		
All Cause	3,220	3,214	1.00	(0.97, 1.04)
All Cancers	805	736	**1.09**	(1.02, 1.17)
Oral Cavity and Pharynx	18	15.0	1.20	(0.71, 1.89)
Esophagus	21	18.6	1.13	(0.70, 1.72)
Stomach	12	24.1	**0.50**	(0.26, 0.87)
Colon	69	77.5	0.89	(0.79, 1.99)
Liver and Gallbladder	20	15.5	1.29	(0.43, 4.0)
Pancreas	33	37.2	0.89	(0.61, 1.25)
Larynx	7	8.8	0.80	(0.32, 1.64)
Lung and Bronchus	330	238.8	**1.38**	(1.24, 1.54)
Mesothelioma	3	0.48	**6.20**	(1.28, 18.1)
Kidney	20	19.5	1.03	(0.63, 1.59)
Bladder	31	24.5	1.26	(0.86, 1.79)
Prostate	70	86.2	0.81	(0.63, 1.03)
Brain	17	17.0	1.00	(0.58, 1.60)
Hodgkin Lymphoma	5	3.7	1.36	(0.44, 3.16)
Non-Hodgkin Lymphoma	24	27.7	0.87	(0.55, 1.29)
Multiple Myeloma	15	12.9	1.16	(0.65, 1.92)
Leukemia	30	30.7	0.98	(0.66, 1.39)
Diabetes Mellitus	54	53.8	1.00	(0.75, 1.31)
Psychiatric Disorders	22	23.2	0.95	(0.60, 1.44)
Nervous System Disorder	57	49.9	1.14	(0.74, 1.86)
Diseases of Digestive System	110	107.8	1.02	(0.86, 1.48)
Cirrhosis	34	36.1	0.95	(0.65, 1.31)
Ischemic Heart Disease	1,049	1,131	**0.93**	(0.87, 0.99)
Cerebrovascular Disease	230	253.9	0.91	(0.79, 1.03)

'Table 3.15 continued'

Mortality	AEC/DOE Observed	IA Expected	SMR	95% CI
Respiratory Disease	336	291.0	**1.15**	(1.03, 1.29)
Pneumonia	104	97.9	1.06	(0.87, 1.29)
COPD	190	149.6	**1.27**	(1.10, 1.46)
Asbestosis	2	0.22	**9.28**	(1.12, 33.5)
Injury	35	41.7	0.84	(0.58, 1.17)
Suicide	32	40.1	0.79	(0.54, 1.11)

Table 3.16 Standardized Mortality Ratios (SMRs) for Female IAAAP Workers
Compared to the Iowa Population, 1951-2005

Mortality	Number of Cases		SMR	95% CI
	AEC/DOE Observed	IA Expected		
All Cause	3,220	3,214	1.00	(0.97, 1.04)
All Cancers	122	86.4	**1.41**	(1.17, 1.69)
Colon	11	11.2	0.98	(0.49, 1.76)
Liver and Gallbladder	5	2.3	2.16	(0.70, 5.04)
Pancreas	6	4.3	0.89	(0.61, 1.25)
Larynx	7	8.77	0.80	(0.32, 1.64)
Lung and Bronchus	35	14.2	**2.47**	(1.72, 3.44)
Breast	20	16.6	1.21	(0.74, 1.86)
Ovary	6	6.0	1.00	(0.37, 2.17)
Brain	4	2.3	1.78	(0.49, 4.56)
Leukemia	4	3.1	1.29	(0.35, 3.30)
Diabetes Mellitus	8	8.5	0.94	(0.41, 1.85)
Psychiatric Disorders	6	4.0	1.48	(0.54, 3.23)
Nervous System Disorders	10	7.9	1.26	(0.60, 2.32)
Diseases of Digestive System	17	11.9	1.43	(0.83, 2.29)
Ischemic Heart Disease	119	90.4	**1.32**	(1.09, 1.58)
Respiratory Disease	41	25.8	**1.59**	(1.14, 2.16)
Pneumonia	9	10.5	0.85	(0.39, 1.62)
COPD	25	10.1	**2.47**	(1.60, 3.65)
Cerebrovascular disease	44	33.0	1.33	(0.97, 1.79)

Table 3.17 Summary of Significant Results for Male AEC/DOE Workers
(Significantly Decreased=D and Significantly Elevated=E)

Summary of Cancer Incidence and Mortality Results	PIR (0-64)	PIR (65+)	SIR	RSIR	SMR (US Ref.)	SMR (IA Ref.)
All Cause					D	
All Cancers			D			E
Oral cavity/Pharynx		E				
Lip						
Brain						
Thyroid						
Esophagus						
Stomach			D		D	D
Liver and Gallbladder						
Pancreas	E					
Urinary Bladder			D			
Kidney			D			
Melanoma						
All Respiratory Cancer					E	
Larynx						
Lung and Bronchus	E	E	D	E	E	E
Pleura (Mesothelioma)		E				E
Male Breast	E					
Colon			D			
Rectum	E					
Prostate	D		D			
Testes		E				
Leukemia						
AML			D			
CLL	E					
CML						
Other Leukemia						

'Table 3.17 continued'

Summary of Cancer Incidence and Mortality Results	PIR (0-64)	PIR (65+)	SIR	RSIR	SMR (US Ref.)	SMR (IA Ref.)
Multiple Myeloma						
Hodgkin Lymphoma						
Non-Hodgkin Lymphoma			D			
Other Cancers			D			
Diabetes Mellitus						
Psychiatric Disorders						
Diseases Urogenital System					D	
Digestive Disease						
Cirrhosis					D	
Heart Disease					D	
Ischemic Disease					D	D
Respiratory Disease					E	E
Pneumonia						
COPD					E	E
Asbestosis						E
Cerebrovascular disease						

Table 3.18 Summary of Significant Results for Female AEC/DOE Workers
(Significantly Decreased=D and Significantly Elevated=E)

Summary of Cancer Incidence and Mortality Results	PIR (0-64)	PIR (65+)	SIR	RSIR	SMR (US Ref.)	SMR (IA Ref.)
All Cause					E	
All Cancers			D		E	E
Oral cavity/Pharynx						
Lip						
Brain						
Thyroid						
Esophagus						
Stomach						
Liver and Gallbladder						
Pancreas	E					
Urinary Bladder						
Kidney						
Melanoma						
All Respiratory Cancer						
Larynx						
Lung and Bronchus					E	E
Pleura (Mesothelioma)						
Female Breast						
Colon						
Rectum						
Ovary						
Cervix		E		E		
Uterus						
Leukemia						
AML						
CLL						
CML		E				

'Table 3.18 continued'

Summary of Cancer Incidence and Mortality Results	PIR (0-64)	PIR (65+)	SIR	RSIR	SMR (US Ref.)	SMR (IA Ref.)
Other Leukemia						
Multiple Myeloma						
Hodgkin Lymphoma						
Non-Hodgkin Lymphoma						
Other Cancers						
Diabetes Mellitus						
Psychiatric Disorders						
Diseases Urogenital System						
Digestive Disease						
Cirrhosis						
Heart Disease						
Ischemic Disease						E
Respiratory Disease						E
Pneumonia						
COPD					E	E
Asbestosis						
Cerebrovascular disease						

CHAPTER FOUR: DISCUSSION

There were four types of analyses performed for this retrospective cancer incidence and mortality study of former AEC/DOE workers at IAAAP: proportional incidence ratios (PIR), standardized incidence ratios (SIR), relative standardized incidence ratios (RSIR) and standardized mortality ratios (SMR). All the results are summarized in Tables 3.17 and 3.18.

Proportional Incidence Ratios

PIR analyses for women demonstrated increased incidence of cancer of the cervix, CML (65+ age group) and pancreas (0-64 age group). All are based on very few cases.

PIR analyses for men in the 0-64 age group showed statistically increased incidence of cancer in several sites: rectum, pancreas, lung, male breast and CLL. Older workers also had a lower incidence of prostate cancer. Men in the 65+ age group had an increased incidence of cancers of the oral cavity/pharynx, lung, mesothelioma and testes.

Men in both age categories showed a statistically significant excess of lung cancer, a total of 153 cases. Women had an elevated incidence of lung cancer as well, but PIRs were not statistically significant. Employees were potentially exposed to multiple carcinogens including radiation, beryllium and asbestos that may have increased their risk of several types of cancer. The smoking history of the AEC/DOE cohort is unknown but tobacco exposure would have increased their risk of lung, cervical, and oropharyngeal cancers.

Overall, proportional studies are most useful as descriptive analyses in cancer epidemiology. PIRs are considered 'numerator data' and are used as a first step before more advanced methods are applied (Breslow and Day, 1987). Generally, these studies are conducted in historical cohorts that have limited demographic information available for the study group. While there is usually adequate data on cancer incidence and

mortality for the cohort, information on an individual's residential history, work exposure, and health history is lacking. PIR results are considered a rough measure of cancer incidence and used only as a guide to examine potential patterns of occurrence. In PIR studies, it is essential to ascertain all cancer cases in the defined cohort otherwise misleading inferences may be drawn. Proportional studies are particularly susceptible to selection bias if follow-up data is incomplete (Breslow and Day, 1987). A proportionate excess can reflect either an excess in the absolute rate for that disease, or a deficit in the absolute rates for some of the other causes (Breslow and Day, 1987).

In the AEC/DOE cohort, cohort identification was difficult because of antiquated employee records. Most of the job history information was taken from the personnel cards, which were often hard to read and had variable record-keeping methods. Cancer incidence was ascertained from Iowa Cancer Registry from 1969-2005 (excluding 1972). Unfortunately, most of the cohort members were employed in the early 1950s, thus missing cancers that have a short-induction period. In the future, intracohort dose-response analyses or a nested case-control study would be needed to investigate the causal relationship between potential exposures at IAAAP and specific cancers of interest.

Standardized Incidence Ratios

Using a different statistical method that includes person-years in the calculation, SIRs were performed to evaluate cancer incidence. Overall, IAAAP AEC/DOE workers had a significantly lower incidence of cancer than the Iowa population. No significant excesses were noted for either men or women. Other cancer incidence studies at DOE sites have found similar results. A cohort of workers from Lawrence Livermore National Laboratory found that the overall cancer incidence is approximately that for the San-Francisco-Oakland area (Austin and Reynolds, 1981). Researchers found a statistically significant excess of melanoma, rectal and salivary gland cancers for women. Male

employees had a statistically higher incidence of melanoma and a lower incidence of lung cancer. Likewise, there were significantly fewer overall cancers based on rates from New Mexico at Los Alamos National Laboratory. They found a lower incidence of smoking-related cancers, particularly lung cancer (2 observed, 19 expected) (Acquavella et al., 1983). Similarly, at IAAAP the SIR for lung cancer was significantly lower for AEC/DOE male employees. The observed lower lung cancer incidence among the DOE studies may be a function of the better education and the higher socioeconomic status of the workers compared to the general population. Smoking has been the primary, well-established risk factor for lung cancer. While, there is no information regarding the prevalence of smoking in this cohort, other tobacco-associated cancers were lower in the AEC/DOE workers (stomach, colon, bladder and kidney cancers).

Another limitation of the SIR analyses was the lack of information on other potential confounding factors, i.e. race, weight, alcohol use and specific workplace exposures. Controlling for these factors may have minimized the influence of these potential confounders since the workers most likely differed from the Iowa population.

Determination of cancer incidence was also limited by lack of incidence data from 1947-1968 and 1972, so person-years calculation started in 1969. No person-years were counted from those earlier years even though a majority of the AEC/DOE cohort was employed in the early 1950s. This may result in an underestimation of cancer incidence since cases with short induction periods or cases that occurred in the younger years may have been missed (the average age at start of employment was 32 years old). The SMR results demonstrate that the mortality from 'all cancers' is significantly elevated in both men and women (Iowa population as reference). Since the SMR results include the earlier time period, some cases of cancer may have been missed in the SIR results.

Another problematic issue was the identification of cause of death, demographic and residential histories of the cohort members. Typically, a thorough historical cohort requires full ascertainment of the workers of interest. The AEC/DOE cohort

identification has been particularly difficult because of the age of the workers, they are older and much more difficult to trace. About one hundred of the AEC/DOE workers were born in the late 1800s and early 1900s, making it difficult to find follow-up information. Some of these men were born when there was no electronic recordkeeping. Even large private databases like LexisNexis were unable to track older members of this cohort. LexisNexis records were generally suboptimal before 1990, especially for individuals who did not have a credit card history. There were approximately 181 death certificates that were unattainable the time of analysis. These were typically men over 100 years of age with no death records. Some of these records may be from Illinois where there has been a freeze on the acquisition of death certificates. Additionally, there were no records available for these workers through the SSA query or any other data source.

There may have been cohort members excluded from the incidence portion of the study due to the inability to prove Iowa residence, this may have influenced the results as well. Additionally, workers may have also left Iowa and developed a cancer in another state which would lead to an under-ascertainment of incident cases. Significant deficits may also be due to the Healthy Worker Effect which is discussed in greater detail in the next section.

<p align="center">Relative Standardized Incidence Ratios</p>

In additional analyses using the SIR results, male workers from the AEC/DOE cohort experienced a statistically significant elevation in lung cancer (RSIR 1.22, 95% CI 1.01-1.47). Female workers had an increased incidence of cervical cancer (RSIR 3.49, 95% CI 1.47-7.13). RSIRs are useful in evaluating whether there is an excess or deficit of cancer cases for each specific cause relative to the overall deficit of cancers in the AEC/DOE subjects. Evidence suggests that cervical cancer is associated with smoking, high parity and human papillomavirus infection (IARC, 2004 and Ho et al., 1998). Little

demographic information is available about the women who worked at IAAAP; however, general U.S. population statistics from this same time period indicate smoking became more popular among women (Borio, 2007).

Smoking, radiation, asbestos and beryllium exposure have all been proven to influence lung cancer risk. These exposures may have varied at IAAAP by job site, job title and employment history. Various workplace protections were employed as occupational safety was prioritized. No other DOE site has experienced an increased risk of lung or cervical cancer in the SIR studies, thus an exploration of workplace related exposures is needed.

<u>Standardized Mortality Ratios</u>

SMRs were calculated from 1947-2005 by collecting causes of death and calculating person-years. AEC/DOE male workers have fewer deaths due to all causes than expected based upon US referent rates. All cause mortality compared to Iowa referent rates was at unity. Other DOE mortality studies have demonstrated similar results for workers due to the Healthy Worker Effect (HWE). Pantex, Rocketdyne and Oak Ridge National Laboratory (ORNL) demonstrated statistically significant lower all cause mortality. Generally, employed populations are healthier when compared to the general population because of medical screenings and better access to health care. The 15-country study of cancer risk among radiation workers in the nuclear industry obtained similar results (Vrijheid et al., 2007). Evaluating all cause mortality by job code, length of employment or by hourly/salaried workers may help control for this HWE. Relative deficits in all cause and all cancer mortality have differed by pay code in other studies of nuclear workers (Richardson et al., 2007). Salaried workers at Savannah River Plant (SRP) exhibited an even lower all cause mortality when compared to the hourly workers.

At IAAAP, male SMRs due to cancer of the stomach, colon, ischemic heart disease and cirrhosis were significantly lower than the US referent rates. Similarly,

compared to the Iowa population, male workers had lower SMRs due to cancer of the stomach and ischemic heart disease. Lower mortality from ischemic heart disease was also found in the Pantex cohort (Acquavella et al., 1982 and 1985). Mortality findings for cardiovascular diseases are particularly difficult to interpret because of HWE (Cho, 1992). Healthier persons (due to lifestyle factors) are more likely to be selected for employment in most industries. There is a high correlation between socioeconomic status (SES) and smoking. Workers may be chosen based on education (correlated with SES) and smoke less at hire, thus having lower prevalence of cardiovascular disease in the future.

At IAAAP, deaths due to lung cancer, diseases of the respiratory system, and COPD were significantly elevated in male and female workers when compared to the US and Iowa general population. Male employees had increase risk of dying from all respiratory cancers when compared to the U.S. population. Interesting findings for men were statistically significant SMRs for asbestosis and mesothelioma (n=2 and n=3, respectively, IA referent rates). Mortality from mesothelioma was greater than expected in workers from SRP as well (Richardson et al., 2007). Compared to IAAAP, workers from SRP experienced similar exposures to ionizing radiation and asbestos. AEC/DOE workers were potentially exposed to asbestos, especially during the early years of construction and renovation. Other possible exposures at the plant that contribute to lung cancer include radiation, beryllium and smoking. If excess in lung cancer and respiratory diseases were due to smoking alone then excesses should be elevated in other diseases related to smoking. Elevated SMRs for diseases such as ischemic heart disease and cancers of the esophagus, bladder, kidney and pancreas may indicate tobacco-related effects (Axelson and Steenland, 1988).

Other DOE sites have documented a lower smoking prevalence among workers. Smoking prevalence was markedly decreased in a cross-sectional study of smoking in male Los Alamos National Laboratory (LANL) employees in the 1980s (Wiggs et al.,

1994 and Mahoney et al., 1987). The authors suggested that nuclear workers at LANL were better educated and more affluent than the general population. Deaths observed in the AEC/DOE workers demonstrated a significant deficit in heart disease but an increase in lung cancer and COPD. These findings suggest there may have been exposures other than smoking related to respiratory disease mortality.

Other DOE sites have experienced increased mortality from lung cancer: ORNL, Hanford, LANL and Rocky Flats National Laboratory (RFNL). RFNL supplied nuclear weapon components to IAAAP and Pantex. In a case-control study, RFNL workers with cumulative internal lung doses of more than 400 mSv (plutonium, americium and uranium isotopes) had a higher risk of lung cancer (Brown et al., 2004). Hanford workers older than 55 years of age demonstrated an excess relative risk of lung cancer with increased cumulative radiation dose (Wing, 2005). Additionally, workers from Zia Company (LANL) and ORNL Y-12 experienced increased SMRs from lung cancer. Increase mortality from lung cancer and respiratory diseases in the AEC/DOE cohort suggests workers may have experienced workplace exposures as well. Priority should be given to organizing and verifying the IAAAP radiation data so significant findings can be investigated further.

Strengths and Weaknesses of Retrospective Cohort Studies

The retrospective cohort study design has been instrumental in the identification of numerous occupational hazards and quantification of workplace risks. Historical cohort mortality and incidence studies allow for the investigation of diseases with prolonged induction and latency periods. Most historical cohorts evaluate cancer mortality as the endpoint of interest; however, as population-based cancer registries have been developed, information on non-fatal cancer outcomes have become available. The primary objective in occupational studies is to first examine temporal patterns of disease through a descriptive study. The advantage to a historical design is the ability to follow

and gather information on a cohort of workers for decades. Because multiple health outcomes can be examined, cohort studies offer the broadest available insight into the health experience of the workforce. There are, however particular disadvantages to retrospective cohort studies. Enumerating and reconstructing an older cohort may be difficult when using industry records. Unavailability of work history, exposures data or health history information is a hindrance to subcohort analysis in occupational studies. Exposure data for workers employed during the early may have been discarded or lost over the years, or may have been collected only on workers thought to be highly exposed. These follow-up issues impacted the AEC/DOE cohort analysis as well. The following sections further review specific strengths and weaknesses of the AEC/DOE cohort.

Strengths of the AEC/DOE Cohort

The essential feature of an historical cohort is the ability to evaluate the development of chronic disease in a defined group over decades of surveillance. Cohort studies generally include all the members of a workforce, not just a sample, allowing for evaluation of health outcomes with long induction and latency intervals. The study design generates data for numerous health outcomes as well. Typically, the results may guide researchers to develop further studies using exposure information. Researchers may also study relatively rare health outcomes, for example mesothelioma in asbestos workers. Generally, historical cohort studies do not incur the cost and time expenses of prospective studies. The AEC/DOE cohort has been evaluated retrospectively, starting in 1947. This type of follow-up would be more difficult in a prospective design due to cost and time restrictions.

Elimination of Certain Types of Bias

One strength of the retrospective cohort design is the avoidance of recall bias. Recall bias is eliminated in historical cohort studies because there is no difference in recall of specific exposures between the exposed and unexposed. In the case of the

AEC/DOE workers, a majority of the group is deceased and specific exposures were not evaluated individually. Moreover, the job dictionary and job exposure matrix are being created independently from the outcomes of interest to avoid over-ascertainment of exposures in cases of incident cancers or specific causes of mortality.

Selection bias is generally eliminated in historical cohorts as well if there is full ascertainment of the group of interest. Problems only arise if there is a difference in follow-up between the exposed and unexposed population. Certain individuals may be harder to trace due to certain lifestyle and socioeconomic factors that may be related to both disease and/or work exposures. Some IAAAP workers were harder to trace because of the age of the cohort, thus it is difficult to quantify if these workers somehow differed by workplace exposure.

Weaknesses of the AEC/DOE Cohort

One of the main drawbacks to a historical cohort is the lack of information available to reconstruct the workforce. Information on the AEC/DOE workers was gathered from the handwritten personnel cards. Some missing or illegible data on individual workers included job title, job code and employment dates. Job codes and dates were handwritten and not recorded in a consistent manner. Job code information would help determine whether workers were hourly or salaried. Hourly and salaried workers may have different work exposures and differ by compensation/medical benefits as well.

About 47% (mortality study) of the employment start dates were missing from the card data and this date was imputed to calculate person-years. The methods of estimating length of employment were described previously. If person-year calculations were underestimated than the actual SMRs would be lower, thus worsening the Healthy Worker Effect (HWE). Additionally, we were unable to stratify on length of employment

or time since first employment; both of these stratification methods lessen the impact of HWE.

Another weakness is the missing data on residential history. Examining and verifying an Iowa residence was imperative for the SIR analysis. The AEC/DOE workers are a selected subgroup of the Iowa (and possibly surrounding states, Illinois and Missouri) populations. If a worker developed a cancer in a surrounding state, this could potentially underestimate the cancer incidence experienced by this cohort. The mortality results were also affected by problems attaining death certificates. Individual death certificates were unattainable in Illinois due to funding issues. Unless there is full ascertainment of the cohort, mortality findings could be artificially low.

Other missing demographic information may have affected the results. Most retrospective cohort studies are able to stratify on race, 35% of this information was missing for the IAAAP workers. SMRs have varied by race at other DOE sites, for example Hispanic and white workers at LANL both experienced higher SMRs but for different causes of death (Galke et al., 1992).

The AEC/DOE workers have limited data available on specific radiologic and chemical exposures. There were some radiation monitoring records available, but only for a small portion of the cohort. There were inadequate records available on potential chemical exposures. Most industrial settings are complex settings with various mixtures of chemical, physical and radiologic exposures. Exposure data from the early, relevant years of production are absent or incomplete. IAAAP released only limited information on the technology employed while manufacturing the nuclear weapons because it is classified material. In addition, there is very limited information on personal protective measures employed during job-related activities, except for information gathered from personal interviews of individual workers.

Moreover, there is an absence of information on potential confounding and effect modifying variables, such as smoking, alcohol use, and family history. Many of the

potential exposures could have additive or multiplicative effects when combined with smoking. For lung cancer induction in the Mayak workers, high levels of smoking and plutonium body burdens had multiplicative effects on risk (Tokarskaya et al., 2002). A review of studies examining the combined effects of asbestos and smoking has also shown that smokers with the highest asbestos exposures have a multiplicative risk of developing lung cancer (Vainio and Pofetta, 1994). Male AEC/DOE employees exhibited lower SMRs for ischemic heart disease and cirrhosis, suggesting there was a lower prevalence of smoking and alcohol abuse. Overall, these workers may have been a healthier, more educated cohort, but further research is needed to verify the results.

Conclusions

A retrospective mortality and cancer incidence study of former nuclear weapons assemblers from the Iowa Army Ammunitions Plant in Burlington, Iowa was conducted. This study examined whether or not workers at the plant exhibited higher rates of mortality or cancer as a result of their work-related activities. Potential exposures included radiation, beryllium, asbestos, and solvents. The SIR and SMR results demonstrated different results; the SIR results were all under unity, yet some of the SMR were above. This is most likely due to the dates of study, as the SMR study includes data from 1947.

In summary, the cancer incidence portion of the study showed overall cancer deficits for both men and women. This may be due to the Healthy Worker Effect and the limited dates of study. There are no cancer registry data before 1969, which likely resulted in missing cancers with short induction periods. Workers may have also moved out of the Iowa area and had a cancer diagnosis in another state. The mortality portion of the study showed men had a lower overall mortality compared to the U.S. population. There was an excess of respiratory disease deaths and deaths from lung cancer in both men and women. Considering the significant respiratory exposures workers may have

experienced and evidence of increased respiratory disease risk, further studies using either a nested case-control or intracohort dose-response design utilizing the JEM is warranted.

REFERENCES

Acquavella JF, Wiggs LD, Waxweiler RJ, et al. Supplementary documentation for an environmental impact statement regarding the Pantex Plant. Occupational Work Force Mortality Study. Los Alamos National Laboratory, 1982.

Acquavella JF, Wilkinson GS, Wiggs LD, et al. Evaluation of cancer incidence among employees at the Los Alamos National Laboratory. Epidemiology applied to health physics conference; 10 Jan 1983; Albuquerque, NM.

Acquavella JF, Wiggs LD, Waxweiler RJ, et al. Mortality among workers at the Pantex Weapons facility. Health Physics 1985;48:735-745.

Adams EE, Braes AM. Breast cancer in female radium dial workers first employed before 1930. J Occup Med 1980;22:586-7.

Agency for Toxic Substances and Disease Registry (ATSDR 1999). Health Consultation. Iowa Army Ammunition Plant. Middletown, Des Moines County, Iowa. EPA facility ID: IA7213820455.Federal Facilities Assessment Branch. Division of Health Assessment and Consultation.

Agency for Toxic Substances and Disease Registry (ATSDR 2003). Health Consultation. Iowa Army Ammunition Plant. Environmental Pathway Evaluation for Beryllium and Depleted Uranium. Middletown, Des Moines County, Iowa. EPA facility ID: IA7213820455. Federal Facilities Assessment Branch. Division of Health Assessment and Consultation.

Agency for Toxic Substances and Disease Registry (ATSDR 2008). Toxicological Profile for Asbestos. CAS # 1332-21-4. Update. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Alberg AJ and Samet JM. Epidemiology of lung cancer. Chest 2003;123:21S-49S.

Alexander V and DiMarco. Reappraisal of brain tumor risk among U.S. nuclear workers: a 10 year review. J Occup Med 2001;16: 289-315.

Alvarez, R. The Risks of Making Nuclear Weapons: A Review of the Health and Mortality Experience of U.S. Department of Energy Workers. Government Accountability Project, Washington, DC, 2000

American Cancer Society (ACS). Cancer facts and figures2001. Atlanta: ACS, 2001.

Andersson M and Storm HH. Cancer incidence among Danish Thorotrast-exposed patients. J Natl Cancer Inst 1992;84:1318-1325.

Armitage JO and Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998;16:2780-2795.

Armstrong BK and Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B Biol 2001;63: 8-18.

Arrighi HM and Hertz-Picciotto I. The evolving concept of the Healthy Worker Survivor Effect. Epidemiology 1994;5:189-196.

Austin DF, Reynolds PJ, Snyder MA, et al. Malignant melanoma among employees of the Lawrence Livermore National Laboratory. Lancet 1981;2:712-716.

Austin DF and Reynolds PJ. Investigation of an excess of melanoma among employees of the Lawrence Livermore National Laboratory. Epidemiology 1997;145:524-531.

Axelson O and Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. Am J of Ind Med 1988;13:105-118.

Baillargeon J, Wilkinson GS. Characteristics of the healthy survivor effect among male and female Hanford workers. Am J Ind Med 1999;35:343-347.

Barnhart S, Keogh J, Cullen MR, et al. The CARET asbestos-exposed cohort: baseline characteristics and comparison to other asbestos-exposed cohorts. Am J Ind Med 1997;32:573-581.

Barnholtz-Sloan JS and Kruchko C. Meningiomas: causes and risk factors. Neurosurg Focus 2007;23:1-8.

BEIR VII, The Committee on the Biological Effects of Ionizing Radiations. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. 2005, National Academy of Sciences, National Research Council. Washington DC: National Academic Press, 2005.

Berry G. Mortality of workers certified by pneumoconiosis medical panels as having asbestosis. Br J Ind Med 1981;38: 130-137.

Blair A and Kazerouni N. Reactive chemicals and cancer. Cancer Causes Control 1997;8:473-490.

Bleise A, Danesi PR, and Burkart W. Properties, use and health effects of depleted uranium (DU): a general overview. J Environ Radioactivity 2003; 64: 93-112.

Boice JD Jr.. Studies of atomic bomb survivors: understanding radiation effects. JAMA 1990;264:622-623.

Boice JD Jr, Cohen SS, Mumma MT, et al. Mortality among radiation workers at Rocketdyne Atomics International, 1948-1999. Radiat Res 2006;166:98-115.

Boice JD Jr, Marano DE, and Cohen SS, et al. Mortality among Rocketdyne workers who tested rocket engines, 1948-1999. J Occup Environ Med 2006a;48:1070-1092.

Borio, G. Tobacco timeline: the twentieth century 1950-1999-the battle is joined. Tobacco BBS (212-982-4645), 2007. Last accessed November 2010: www.tobacco.org.

Bosch FX, Ribes J, Diaz M, et al. Primary liver cancer: worldwide incidence and trends. Gastroenterology 2004;127:S5-S16.

Breslow NE and Day NE, 1987. Statistical Methods in Cancer Research. Volume II-The Design and Analysis of Cohort Studies. World Health Organization, IARC scientific publication No. 82: Oxford University Press, New York.

Breysse PN, Weaver V, Cadorette M, et al. Development of a medical examination program for former workers at a Department of Energy National Laboratory. Am J Ind Med 2002;42:443-454.

Brown SC, Schonbeck MF, McClure D, et al. Lung cancer and internal lung doses among plutonium workers at the Rocky Flats Plant: a case-control study. Am J Epidemiol 2004;160:163-172.

Burkhart W. Radioepidemiology in the aftermath of the nuclear program of the former Soviet Union: unique lessons to be learnt. Radiat Environ Biophys 1996;35:36-73.

Cardis E, Gilbert ES, Carpenter L, et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. Radiat Res 1995;142:117–132.

Cardis E, Vrijheid M, Blettner M, et al. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. Br Med J 2007;331:77-80.

Carmichael P, Lieben J. Sudden death in explosives workers. Archives in Environmental Health. 1963;63:424-439.

CDC, document 2001-133. Occupational Energy Research Program. Department of Health and Human Services. Center for Disease Control and Prevention. NIOSH. See http://www.cdc.gov/niosh/docs/2001-133/pdfs/2001-133.pdf , last accessed April 2010.

Checkoway H, Mathew RM, Shy CM, et al. Radiation, work experience, and cause specific mortality among workers at an energy research laboratory. British Journal of Industrial Medicine 1985;42:525-533.

Checkoway H, Pearce N, Crawford-Brown DJ, et al. Radiation doses and cause-specific mortality among workers at a nuclear materials fabrication plant. Am J Epidemiol 1988;127:255–66.

Checkoway H, Pearce N, Kriebel D. Research Methods in Occupational Epidemiology, 2nd ed. New York: Oxford University Press 2004.

Cho BCK. Definition, sources, magnitude, effect modifiers, and strategies of reduction of the healthy worker effect. J Occup Med 1992;34:979-988.

Christenson PJ, Craig JP, Bibro MC et al. Cysts containing renal cell carcinoma in von Hippel-Lindau diseases. J Urol 1982; 128: 798-800.

Christenson LJ, Borrowman TA, Vachon CM, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA 2005; 294: 681-690.

Cologne JB, Tokuoka S, Beebe GW, et al. Effects of radiation on incidence of primary liver cancer among atomic bomb survivors. Radiat Res 1999;152:364-373.

Coultas DB and Samet JM. Occupational lung cancer. Clin Chest Med 1992:13:341-354.

Cowper DC, Kubal JD, Maynard C, et al. A primer and comparative review of major U.S. mortality databases. Ann Epidemiol 2002;12:462-468.

Cragle DL, McLain RW, Qualters JR, et al. Mortality among workers at a nuclear fuels production facility. Am J Ind Med 1988;14:379-401.

Cragle DL, Watkins JP, Ingle N, et al. Mortality Among a Cohort of White Male Workers at a Uranium Processing Plant: Fernald Feed Materials Production Center, 1951-1989. Oak Ridge, TN: Center for Epidemiologic Research, Oak Ridge Institute for Science and Education [1995]. Unpublished.

Cugell DW, Kamp DW. Asbestos and the pleura: a review. Chest 2004;125:1103-1117.

Davie L and Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-2167.

Day and Zimmerman. Munitions Products and Services. 2004. Available at http://www.dayzim.com/Services/Munitions Accessed June, 2007.

Dement JM, Ringen K, Welch LS, et al. Mortality of older construction and craft workers employed at Department of Energy (DOE) nuclear sites. Am J Ind Med 2009;52:671-682.

Doll R and Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the U.S. today. J Natl Cancer Inst 1981;66:1191-1308.

DOE [1999]. Comprehensive epidemiologic data resource. Washington, DC: U.S Department of Energy, Office of Epidemiology Studies, p.48.

DuPree AE, Cragle D, McLain RS, et al. Mortality among workers at a uranium processing facility, the Linde Air Products Company Ceramics Plant 1943-49. Scandinavian Journal of Work, Environment & Health 1987;13:100-107.

Dupree EA, Wells SM, Watkins JP, Wallace PW, Davis NC [1994]. Mortality among workers employed between 1945 and 1984 at a uranium gaseous diffusion facility. Oak Ridge, TN: Center for Epidemiologic Research Medical Sciences Division; Oak Ridge Institute for Science and Education; (DOE Contract DE-AC05-760R00033, Final report.) Available from the National Institute for Occupational Safety and Health/Health-Related Energy Research Branch, Cincinnati, OH, 24 pg.

Dupree-Ellis E, Watkins J, Ingle N, et al. External radiation exposure and mortality in a cohort of uranium processing workers. Am J of Epidemiol 2000;152:91-95.

Franklyn JA, Maisonneuve P, Sheppard M, et al. Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. Lancet 1999;353:2111-2115.

Fraser P, Carpenter L, Maconochie N, et al. Cancer mortality and morbidity in employees of the United Kingdom Atomic Energy Authority, 1946–86. Br J Cancer 1993;67:615–24.

Fritz A, et al, eds. 2000. World Health Organization, International Classification of Disease for Oncology, 3rd. ed., World Health Organization, Geneva.

Frome EL, Cragle DL, Watkins JP, et al. A mortality study of employees of the nuclear industry in Oak Ridge, Tennesee. Radiat Res 1997;148:64-80.

Fry SA. Studies of U.S. radium dial workers: an epidemiological classic. Radiat Res 1998;150:s21-s29.

Fuortes, L. Needs Assessment, Burlington Atomic Energy Commission Plant – Former Worker Program, 2001.

Fuortes L, 2006. The Energy Employees Occupational Illness Compensation Program Act: Are We Fulfilling the Promise We Made to Cold War Veterans When We Created the Program (Part IV). Testimony before the House Committee on the Judiciary Subcommittee in Immigration, Border Security, and Claims Oversight Hearing. Last Accessed May 2010: http://cph.uiowa.edu/IowaFWP/documents/Fuortes_testimony.pdf.

Furukawa K, Preston DL, Lonn S, et al. Radiation and smoking effects on lung cancer incidence among atomic bomb survivors. Radiat. Res 2010;174:72–82.

Galke GA, Johnson ER, Tietjen GL. Mortality in an ethnically diverse radiation exposed occupational cohort. Los Alamos, NM: Los Alamos National Laboratory 1992; unpublished.

Gardner MJ. Considerations in the choice of expected numbers for appropriate comparisons in occupational cohort studies. Med Lav 1986;77:23-47.

Gilbert ES, Peterson GR, Buchanan JA. Mortality of workers at the Hanford Site: 1945 1981. Health Phys 1989a;56:11-25.

Gilbert ES, Fry SA, Wiggs LD, et al. Analyses of combined mortality data on workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Nuclear Weapons Plant. Radiat Res 1989b;120:19-35.

Gilbert ES, Omohundro E, Buchanan JA,Holter NA. Mortality of workers at the Hanford Site: 1945-1986. Health Phys 1993a;64:577-590.

Gilbert ES, Cragle DL, Wiggs LD, et al. Updated analyses of combined mortality data for workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Nuclear Weapons Plant. Radiat Res 1993b;136:408-21.

Gilbert ES, Koshurnikova NA, Sokolnikov M, et al. Liver cancers in Mayak workers. Radiat Res 2000;154:246–52.

Glass AG and Hoover RN. The emerging epidemic of melanoma and squamous cell skin cancer. JAMA 1989; 262: 2097-2100.

Glass DC, Gray CN, Jollet Dj, et al. Leukemia risk associated with low-level benzene exposure. Epidemiology 2003; 14: 569-577.

Goodwin J. Twenty years handling TNT in a shell loading plant. Am Ind Hyg Assoc J 1972; 33:41-44.

Gordon I, Boffetta P, Demers PA. A case study comparing a meta-analysis and a pooled analysis of studies of sinonasal cancer among woodworkers. Epidemiology 1998;9:518-524.

Hall HI, Miller DR, Rogers JD et al. Update on the incidence and mortality from melanoma in the United States. J Am Acad Dermat 1999; 40: 35-42.

Hathaway JA. Trinitrotoluene: a review of reported dose-related effects providing documentation for a workplace standard. J. Occup. Med. 1977,19:341-345.

Heineman EF, Cocco P, Gomez MR, et al. Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. Am J Ind Med 1994;26; 155-1969.

Hempelmann LH, Langham WH, Richmond CR, et al. Manhattan Project plutonium workers: a twenty-seven year follow-up study of selected cases. Health Phys 1973;25:461-479.

Hernberg S, Westerholm P, Schultz-Larsen K, et al. Nasal and sinonasal cancer: connection with occupationalexposures in Denmark, Finland and Sweden. Scand J Work Environ Health 1983;9:315-326.

Hillerdal G. Pleural plaques and the risk for bronchial carcinoma and mesothelioma. Chest 1994; 105;144-150.

Hillerdal G and Ozesmi M. Benign asbestos pleural effusion: 73 exudates in 60 patients. Eur J Resp Dis 1987; 71: 113-121.

Hillerdal G. Rounded atelectasis. Clinical appearance with 74 patients. Chest 1989; 95: 836-841.

Ho GY, Kadish AS, Burk RD, et al. HPV 16 and cigarette smoking as risk factors for high-grade cervical intra-epithelial neoplasia. Int J Cancer 1998;78:281-855.

Hogstedt C, Rohlen O, Berndtsson BS, et al. A cohort study of mortality and cancer incidence in ethylene oxide production workers. Br J of Indust Med 1979;36:276-280.

Hohryakov VF, Romanov SA. Lung cancer in radiochemical industry workers. Sci Total Enviro 1994;142:25-28.

Howe GR. Cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose rate ionizing radiation in the Canadian Fluoroscopy Cohort Study and a comparison with mortality in Atomic Bomb Survivors Study. Radiat Res 1995;142:295-304.

IARC, International Association for Research on Cancer, Lyon, 2004. Tobacco smoke and Involuntary Smoking. Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol.83. World Health Organization.

Iowa Ordnance Plant (IOP). Occupational Disease Report-IA 200.5/141. June 18, 1943.

Ivanov VK, Gorski AI, Tsyb AF, et al. Solid cancer among emergency workers residing in Russia: estimation of radiation risks. Radiat Environ Biophys 2004;43:35-42.

Infante P, Newman L. Beryllium exposure and chronic beryllium disease. Lancet 2004;363:415-416.

Ismail-Khan R, Robinson LA, Williams CC, et al. Malignant pleural mesothelioma: a comprehensive review. Cancer Control 2005;13:255-263.

Kahn K, Ryan K, Sabo A, et al. Ionizing radiation. In: Levy BS, Wegman DH, eds. Occupational Health. Boston: little, Brown, 1983;189-206.

Kaldor JM, Day NE, Kittekmann B, et al. Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: a case control study. Int J Cancer 1995;63:1-6.

Karlsson P, Holmberg E, Lundell M, et al. Intracranial tumors after exposure to ionizing radiation during infancy: a pooled analysis of two Swedish Cohorts of 28,008 infants with skin hemangiomas. Radiat Res 1998;150:357-364.

Kathren RL and Moore RH. Acute accidental exposure of uranium: a 38 year follow-up. Health Phys 1986;51:609-619.

Kathren RL, McInroy JF, Moore RH, et al. Uranium in the tissues of an occupationally-exposed individual. Health Phy 1989; 57: 17-21.

Kee ST, Gamsu G and Blanc P. Causes of pulmonary impairment in asbestos-exposed individuals with diffuse pleural thickening. Am J Respir Crit Care Med 1996; 154: 789-793.

Khokhriakov VF, Romanov SA. Lung cancer in radiochemical industry workers. Sci Total Enviro 1994;142:25-28.

Khokhriakov VF, Killerer AM, Kreisheimer M, et al. Lung cancer in nuclear workers of Mayak. Radiat Environ Biophys 1998;37:11-17.

Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 2005; 66: s4-s34.

Kogevinas M, Nannetje A, Cordier S, et al. Occupation and bladder cancer among men in Western Europe. Cancer Causes, Control 2003;14 :907-914.

Koshurnikova NA, Buldakov LA, Bysogolov GD, et al. Mortality from malignancies of the hematopoietic and lymphatic tissues among personnel of the first nuclear plant in the USSR. Sci Total Enviro 1994;142:19-23.

Koshurnikova NA, Bysogolov GD, Bolotnikova MG, et al. Mortality among personnel who worked at the Mayak complex in the first years of its operation. Health Phys 1996;71:90–3.

Koshurnikova NA, Buldakov LA,Lyin LA, et al. Lung cancer risk due to exposure to incorporated plutonium. Health Phys 1998;149:366-71.

Koshurnikova NA, Gilbert ES, Sokolnikov M, et al. Bone cancers in Mayak workers. Radiat Res 2000;154:237–45.

Kossman SE and Weiss MA. Acute myelogenous leukemia after exposure to strontium-89 for the treatment of adenocarcinoma of the prostate. Cancer 2000;88;620-624.

Kreisheimer M, Koshurnikova NA, Nekolla E, et al. Lung cancer mortality among male workers of the Mayak facility in the former Soviet Union. Radiat Res 2000;15:3-11.

Land CE. Studies of cancer and radiation dose among atomic bomb survivors: the example of breast cancer. JAMA 1995;274:402-7.

Legler JM, Ries LA, Smith MA, et al. Cancer surveillance series: brain and other nervous system cancers: recent trends in incidence and mortality. J Natl Cancer Inst 1999;91:1382-1390.

Lemert A. A-Bombs, Missiles, and Gravel Gerties. In: First You Take a Pick and Shovel– The Story of the Mason Companies. The John Bradford Press. 160-189. 1979.

Leonowich JA, Bihl A, Dillard JF, et al. Technical Basis Document for Atomic Energy Operations at the Iowa Army Ammunition Plant (IAAP). NIOSH Dose Reconstruction Project, 2004. Document Number: ORAUT-TKBS-0018.

Levine R, Andjelkovich D, Kersteter S, et al. Excessive mortality from ischemic heart disease in men exposed to dinitrotoluene at two ammunition plants. La Medicina del Lavoro. 1986;77:88-89.

Li J, Jiang Q, Zhong W. Persistant ethanol drinking increases liver injury induced by trinitrotoluene exposure: an in-plant case-control study. Human & Experimental Toxicology. 1991;10:405-409.

Lichter MD, Karagas MR, Mott LA et al. Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire Skin Cancer Study Group. Arch Dermatol 2000;136:1007-1011.

Linet MS, McLaughlin JK, Hsing AW et al. Cigarette smoking and leukemia: results from the Lutheran Brotherhood Cohort Study. Cancer Causes and Control 1991;2 413-417.

Linet MS, Schubauer-Berigan MK, Weisenburger DD, et al. Chronic lymphocytic leukaemia: an overview of aetiology in light of recent developments in classification and pathogenesis. British Journal of Haemotalogy 2007;139:672-686.

Liu T and Soong S. Epidemiology of malignant melanoma. Surgical clinics of North America 1996;76:1205-1222.

Loomis DP, Wolf SH. Mortality of workers at nuclear materials production plant at Oak Ridge, Tennessee, 1947-1990. American Journal of Industrial Medicine 1996;29:131-141.

Lubin JH, Boice JD Jr, Edling C, et al. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. J Natl Cancer Inst 1995;87:817-827.

Luc D, Leclerc A, Bergin D. Sinonasal cancers and occupational exposures: a pooled analysis of 12 case-control studies. Cancer Causes Control 2002;13:147-157.

Luce D, Gerin M, Lecler A. Sinonasal cancers and occupational exposure to formaldehyde and other substances. Int J Cancer 1993;53:224-231.

Mahoney MC and Wilkinson GS. Smoking patterns among Los Alamos National Laboratory Employees. Los Alamos National Laboratory Employees. Los Alamos, NM: Los Alamos National Laboratory; Report LA-10650;1987.

Maier H and Tisch M. Epidemiology of laryngeal cancer. Results of the Heidelberg case-control study. Acta Otolaryngol (Stockh) 1997; Suppl 527: 160-164.

Makie T, Adcock D, Lackland, et al. Pulmonary abnormalities associated with occupational exposures at the Savannah River Site. Am J Ind Med 2005; 48: 365-372.

Mancuso TF, Stewart AM, Kneale GW. Radiation exposures of Hanford workers dying from cancer and other causes. Health Physics 1977;33:369-385.

Mancuso, TF. Methodology in industrial health studies: social security disability data and the medical care system. American Journal of Industrial Medicine 1993;23:653-671.

Mason & Hanger-Silas Mason Co. Inc. Report of actions to intensify and expand the safety program to improve safety conditions. Contract No. DAAA09-68-C-0468. Iowa Army Ammunition Plant, 1969.

Mason & Hanger-Silas Mason Co. Inc. Middletown, IA – Survey Summary. Last Revised 4/14/2003. Available at: http://www.bmpcoe.org/bestpractices/external/mash/summary.html Accessed June, 2007.

McCredie M, Ford JM, Stewart JH. Risk factors for cancer of the renal parenchyma. Int J Cancer 1988;42:13-16.

McDiarmid MA. Depleted uranium and public health. Fifty years' study of occupational exposure provides little evidence of cancer. BMJ 2001;322:123-124.

McDiarmid MA, Engelhardt S, Oliver M, et al. Health effects of depleted uranium on exposed Gulf War veterans: a 10-year follow-up. J of Tox Environ Health 2004;67:277-296.

McGregor DH, Land CE, Choi K, et al. Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1969. J Natl Cancer Inst 1977;59:799-811.

McGlynn KA, Tsao, Hsing AW, et al. International trends and patterns of primary liver cancer. Int J Cancer 2001:94;290-296.

Mikkelsen S, Joergensen M, Browne E, et al. Mixed solvent exposure and organic brain damage. Acta Neurol Scand 1988;78:s118.

Mikulski MA, Leonard SA, Sanderson WT, et al. Risk of beryllium sensitization in a low-exposed former nuclear weapons cohort from the cold war era. Am J Ind Med (early online) 2010;1-11.

Miller DL and Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. J Am Acad Dermatol 1994;30:774-778.

Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004. Cancer 2009;115:1531-1543.

Morton W. Occupational habituation to aliphatic nitrates and the withdrawal hazards of coronary disease and hypertension. Journal of Occupational Medicine. 1977;19:197-200.

Narbutt J, Lesiak A Erkiert A, et al. Non-melanoma skin cancer development and environmental factors. Pol J Environ Stud 2005;14:545-550.

National Research Council (NRC 1990). Committee on the Biological Effects of Ionizing Radiation, Health Effects on Populations of Exposure to Low Levels of Ionizing Radiation (BEIR V). National Academy of Sciences, Washington, DC.

National Research Council (NRC 2006). Review of the worker and public health activities program administered by the Department of Energy and the Department of Health and Human Services. Nuclear and Radiation Studies Board. Board on Environmental Studies and Toxicology. Division on Earth and Life Studies. The National Academies Press; Washington, D.C.

Neglia JP, Meadows AT, Robinson LL et al. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325: 1330-1336.

Nisse C, Lorthois C, Dorp V, et al. Exposure to occupational and environmental factors in myelodysplastic syndromes- preliminary results of a case-control study. Leukemia 1995; 9: 693-699.

Pacini F, Vorontsova T, Demidchhik EP, et al. Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. J Clin Endocrinol Metab 1997; 82: 3563-3569.

Pershagen G. The carcinogenicity of arsenic. Environ Health Perspect 1981;40:93-100. Picci P. Osteosarcoma (osteogenic sarcoma). Orphanet Journal of Rare Diseases 2007; 2:6.

Pierce DA, Shimizu Y, Preston, et al. Studies of the mortality of atomic bomb survivors. Report 12, part I. Cancer: 1950-1990. Radiat. Res 1996;146:1-27.

Preston DL, Ron E, Tokuoka S, et al. Solid Cancer Incidence in Atomic Bomb Survivors: 1958-1998. Radiation Research 2007;168:1-64.

Preston DL, Kusumi S, Tomonaga M, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. Radiat Res 1994;137:s68-s97.

Redmond CK, Ciocco A, Lloyd JW et al. Long-term mortality study of steelworkers. VI- Mortality from malignant neoplasms among coke oven workers. J Occup Med 1972;14: 621-629.

Reis LG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review, 1973-1998. Bethesda, Maryland: National Cancer Institute; 2001.

Rericha V, Kulich M, Rericha A, et al. Incidence of leukemia, lymphoma, and multiple myeloma in Czech uranium miners; a case-cohort study. Environmental Health Perspectives 2006;114:818-822.

Reynolds PJ and Austin DF. Cancer Incidence among employees of the Lawrence Livermore National Laboratory 1969-1980. The Western Journal of Medicine 1985;142:214-218.

Richardson DB and Wing S. Greater sensitivity to ionizing radiation at older age: follow-up of workers at Oak Ridge National Laboratory through 1990. Int J of Epidemiol 1999;28:428-431.

Richardson DB and Wing S. Leukemia mortality among workers at the Savannah River Site. Am J Epi 2007;166:1015-1022.

Richardson DB, Wing S, and Wolf S. Mortality among workers at the Savannah River Site. Am J Ind Med 2007;50:881-891.

Rinsky RA, Smith AB, Hornung RW, et al. Benzene and leukemia. An epidemiologic risk assessment. New Eng J of Med 1987; 316:1044-1050.

Rinsky RA, Hornung RW and Silver SR. Benzene exposure and hematopoietic mortality: a long-term epidemiologic risk assessment. Am J Indust Med 2002;42 474-480.

Ritz B. Cancer mortality among workers exposed to chemicals during uranium processing. J Occup Env Med 1999;41:556-566.

Ritz B, Morgenstern H, Froines J, et al. Effects of exposure to external ionizing radiation on cancer mortality in nuclear workers monitored for radiation at Rocketdyne/Atomics International. American Journal of Industrial Medicine 1999a;35:21-31.

Ritz B, Morgenstern H, Crawford-Brown D, et al. The effects of internal radiation exposure on cancer mortality in nuclear workers at Rocketdyne/Atomics International. Environmental Health Perspectives 2000;108:743-751.

Robinson BWS, Lake RA. Advances in malignant mesothelioma. N Engl J Med 2005;353:1591-1603.

Rodrigues EG, McClean MD, Weinberg J, et al. Beryllium sensitization and lung function among former workers at the Nevada Test Site. Am J Ind Med 2008;51:512-523.

Ron E. Thyroid Cancer. In: Schottenfeld D, Fraumeni JF, eds. Cancer Epidemiology and Prevention. New York: Oxford University Press, 1996.

Ron E, Lubin JH, and Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995;141:259-277.

Ron E, Preston DL, and Kishikawa M. Skin tumor risk among atomic-bomb survivor in Japan. Cancer Causes. Control 1998; 9; 393-401.

Rosenstock, LR, Cullen MR, Brodkin CA. Textbook of Clinical Occupational and Environmental Medicine, Second Edition. Elsevier Saunders, Philadelphia, PA. 2005.

Rowland RE, Stehney AF, Lucas AF Jr. Dose-response relationships for female radium dial workers. Radiat Res 1978;76 : 368-383.

Samet JM. Radon and lung cancer. J Natl Cancer Inst 1989;81:745-757.

Sanderson WT, Leonard S, Ott D, et al. Beryllium surface levels in a military ammunition plant. J Occup Environ Hyg 2008;5:475–481.

Saracci R, Boffetta P. Interactions of tobacco smoking and other causes of lung cancer. In: Samet JM, ed. Epidemiology of lung cancer. New York, NY: Marcel Dekker, 1994;465-493.

Sato A and Nakajima T. Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br J Ind med 1979;36:231-234.

Savitz DA and Andrews KW. Review of epidemiological evidence on benzene and lymphatic and hematopoietic cancers. Am J Int Med 1997;31: 287.

Schneider AB, Recant W, Pinsky SM, et al. Radiation-induced thyroid carcinoma. Ann Intern Med 1986;105:405-412.

Schneider AB. Radiation-induced thyroid tumors. Endocrinol Metab Clin North AM 1997;19:637-648.

Schubauer-Berigan MK, Daniels RD, and Pinkerton LE. Radon exposure and mortality among White and American Indian uranium miners: an update of the Colorado Plateau Cohort. Am J of Epi 2009;169:718-730.

Selikoff IJ, Hommond EC, Seidman HA. Mortality experience of insulation workers in the United States and Canada, 1948-1976. Ann N Y Acad Med 1979;330:91-116.

Shimizu Y, Schull WJ, Kato H. Cancer risk among atomic bomb survivors: the RERF Life Span Study. JAMA 1990;264:601-604.

Shannon RE and Strayer DS. Arsenic-induced skin toxicity. Hum Toxicol 1989;8:99-104.

Shipley JL and Butera JN. Acute myelogenous leukemia. Experimental Leukemia 2009;37: 649-658.

Shintani T, Hayakawa N, Hoshi M, et al. High incidence of meningioma among Hiroshima atomic bomb survivors. J Radiat Res 1999;40:49-57.

Shore RE. Radiation-induced skin cancers in humans. Med Pediatr Oncol 2001; 36:549.

Shore RE, Hildreth N, Dvoretsky P, et al. Benign thyroid adenomas among persons X-irradiated in infancy for enlarged thymus glands. Radiat Res 1993;134:217-223.

Silver SR, Anderson-Mahoney P, Burphy J, Hiratzka S, Schubauer-Berigan MK, Waters KM [2005]. Mortality Update for the Pantex Weapons Facility: Final Report (NIOSH Intramural Study). Available from the National Institute for Occupational Safety and Health/Health-Related Energy Research Branch, Cincinnati, OH, 31 pgs.

Sison RF, Hruban RH, Moore GW, et al. Pulmonary disease associated with pleural 'asbestos' plaques. Chest 1989;95: 831-835.

Smith H. Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Ann ICRP 1991; 21:1-3.

Smith PG, Douglas AJ. Mortality of workers at the Sellafield plant of British Nuclear Fuels. Br. J. Ind. Med. 1986;42:525-533.

Stange AW, Furman FJ, and Hilmas DE. Rocky Flats Beryllium Health Surveillance. Environ Health Perspect 1996;104; s981-986.

Stange AW, Hilmas DE, Furman FJ. Beryllium sensitization and chronic beryllium disease at a former nuclear weapons facility. Applied Occupational and Environmental Hygiene 2001;16: 405-417.

Stayner L, Dannenberg A, Thun M, et al. Cardiovascular mortality among munitions workers exposed to nitroglycerin and dinitrotoluene. Scandinavian Journal of Work, Environment & Health. 1992;18;34-43.

Stayner L, Dannenberg A, Bloom T, et al. Excess hepatobiliary cancer mortality among munitions workers exposed to dinitrotoluene. Journal of Occupational Medicine. 1993;35:291-296.

Stebbings IH, Lucas HF, Stehney AF. Mortality from cancers of major sites in female radium dial workers. Am J Ind Med 1984;5:4335-59.

Steenland K, Beaumont J, Halperin W. Methods of control for smoking in occupational cohort mortality studies. Scand J Wok Environ Health 1984;10:143-149.

Steenland K and Palu S. Cohort mortality study of 57,000 painters and other union members: a 15 year update. Occup Environ Med 1999; 56:315-321.

Steenland K, Stayner L and Deddens J. Mortality analyses in a cohort of 18,235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup Environ Med 2004;61:2-7.

Stewart AM, Kneale GW. Relations between age at occupational exposure to ionising radiation and cancer risk. Occupational and Environmental Medicine 1996;53:225-230.

Sunderman FW Jr, Morgan LG, Anderson A, et al. Histopathology of sinonasal and lung cancers in nickel refinery workers. Ann Clin Lab Sci 1989;19:44-50.

Tchounwou PB, Newsome C, Glass K, et al. Environmental toxicology and health effects associated with dinitrotoluene exposure. Reviews on Environmental Health 2003; 18: 203-229.

Thompson DE, Mabuchi K, Ron E, et al. Cancer incidence in atomic bomb survivors. Part II: solid tumors, 1958-1987. Radiat Res 1994;137:s17-s67.

TN & Associates, Inc (TNA). 2002. Line 1 and Firing Site Supplemental Remedial Investigation Report, Iowa Army Ammunition Plant. Oak Ridge, Tennessee; prepared for the US Army Corps of Engineers, Omaha District; August 2002.

Tokarskaya ZB, Okladnikova ND, Belyaeva ZD, et al. The influence of radiation and nonradiation factors on the lung cancer incidence among workers of the nuclear Enterprise Mayak. Health Phys 1995;69:356-66.

Tokarskaya ZB Okladnikova ND, Belyaeva ZD, et al. Multifactorial analysis of lung cancer dose-response relationships for the workers at Mayak Nuclear Enterprise. Health Phys 1997;73:899-905.

Tokarskaya ZB, Scott BR and Zhuntova GV et al. Interaction of radiation and smoking in lung cancer induction among workers at the Mayak nuclear enterprise. Health Phys 2002;6:833-846.

Tseng WP, Chur Hm, How SW. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwam. J Natl Cancer Inst 1968; 40:

UNSCEAR, United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. UNSCEAR 2000 Report to the General Assembly With Annexes. New York: United Nations, 2000.

U.S. Army Corps of Engineers (USACOE). 2001. Preliminary Assessment for the Iowa Army Ammunition Plant, St. Louis District Office, St. Louis, Missouri; December 2001.

United States Environmental Protection Agency (US EPA, 2010). Contaminants of Concern at Iowa Army Ammunition Plant, (EPA ID: IA7213820445). Superfund Information Systems. Last accessed November 2010 at: http://cfpub.epa.gov/supercpad/SiteProfiles/index.cfm?fuseaction=second.Contams&id=0 700413.

Vainio H and Pofetta P. Mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer. Scand J Work Environ Health 1994;20:235-242.

Vamvakas S, Brunihng T, Thomasson B et al. Renal cell cancer correlated with occupational exposure to trichloroethene. J Cancer Res Clin Oncol 1998;124:374-382.

Viet SM, Torma-Krajewski J, and Rogers J. Chronic beryllium disease and beryllium sensitization at Rocky Flats: a case-control study. Am Ind Hyg Assoc J 2000; 61:244-254.

Vinneas P, Thomas T, Hayes R, et al. Proportion of lung cancers in males due to occupation in different areas of the U.S. Int J Cancer 1988;42:851-856.

Voelz GL, Hempelmann LH, and Lawrence JNP. A 32-year medical follow-up of Manhattan Project Plutonium Workers. Health Physics 1979;37:445-485.

Voelz GL, Grier RS, Hempelmann LH, et al. A 37-year medical follow-up of Manhattan Project Plutonium Workers. Health Physics 1985;48:249-259.

Voelz GL and Lawrence JNP. A 42-year medical follow-up of Manhattan Project Plutonium Workers. Health Physics 1991;61:181-191.

Voelz GL, Johnson ER, and Lawrence JNP. Mortality of 224 male workers exposed to plutonium, Los Alamos, NM: Los Alamos National Laboratory 1993; unpublished.

Vrijheid M, Cardis E, Blettner M, et al. The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: design, epidemiological methods and descriptive results. Radiation Research 2007;167:361-379.

Ward E, Okun A, Ruder A, et al. A mortality study of workers at seven beryllium processing plants. Am J Ind Med 1992;22:885-904.

Wartenberg D, Reyner D, Scott CS. Tricholorethylene and cancer: epidemiological evidence. Environ Health Perspect 2000;108: s161-176.

Watkins J, Cragle D, Frome E, et al. Collection, validation, and treatment of data for a mortality study of nuclear industry workers. Appl Occup Environ Hyg 1997;12:195-205.

Welch L, Ringen K, Bingham E, et al. Screening for beryllium disease among construction trade workers at Department of Energy nuclear sites. Am J Ind Med 2004;46:207-218.

West RR and Stafford DA. Occupational exposures and haematologic abnormalities among ordnance factory workers: a case-control study. Leukemia Research 1997;2:675-680.

White RF and Proctoc SP. Solvents and neurotoxicity. The Lancet 1997;349:1239-1243.

World Health Organization (WHO). 2001. Depleted Uranium, Sources, Exposures, and Health Effects. Department of Protection of the Human Environment, World Health Organization, Geneva, April 2001

Wick RR, Nekolla EA, Gossner W, et al. Late effects in ankylosing spondylitis patients treated with 224Ra. Radiat Res 1999;152: s8-s11.

Wiggs LD, Cox-Devore CA, and Voelz G. Mortality among a cohort of workers monitored for polonium-210 exposure:1944-1972. Health Physics 1991;61:71-76.

Wiggs LD, Cox-Devore CA, Wilkinson GS, et al. Mortality among workers exposed to external ionizing radiation at a nuclear facility in Ohio. J Occup Med 1991a;33:632-637.

Wiggs LD, Johnson ER, Cox-Devore CA, et al. Mortality through 1990 among white male workers at the Los Alamos National Laboratory: considering exposures to plutonium and external ionizing radiation. Health Phys 1994;67:577–88.

Wilkinson GS, Tietjen GL, Wiggs LD, et al. Mortality among plutonium and other radiation workers at a plutonium weapons facility. Am J Epidemiol 1987;125:231–50.

Wing S, Shy CM, Wood JL, et al. Mortality among workers at Oak Ridge National Laboratory. Evidence of radiation effects in follow-up through 1984. JAMA 1991;265:1397-1403.

Wing S, Shy CM, Wood JL, et al. Job factors, radiation and cancer mortality at Oak Ridge National Laboratory: follow-up through 1984. Am J Ind Med 1993;23:265-79.

Wing S, West CM, Wood JL, et al. Recording of external radiation exposures at Oak Ridge National Laboratory: implications for epidemiologic studies. J Exp Anal Environ Epidemiol 1994;4:83-93.

Wing, S and D.B. Richardson. Age at exposure to ionising radiation and cancer mortality among Hanford workers: follow up through 1994. Occup Environ Med 62:465-472.

Wogan, G. Impact of chemicals on liver cancer risk. Seminars in Cancer Biology 2000;10:201-210.

Wong O, Whorton MD, and Foliart DE, et al. An industry-wide study of Vinyl Chloride Workers, 1942-1982. Am J Ind Med 1991;20:317-334.

Wrensch M, Minn Y, Chew T et al. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro-Oncology 2002; 4:278-299.