



A Nested Case-Control Study of Leukemia and Ionizing Radiation at the Portsmouth Naval Shipyard

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health



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Ionizing Radiation at the Portsmouth Naval Shipyard

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Preface

Ionizing radiation and its sources are used every day in medical, industrial and governmental facilities around the world. Although some health risks from ionizing radiation exposures are widely recognized, the association of these exposures to specific diseases, especially various types of cancer, remains uncertain. Workers at U.S. Department of Energy (DOE) facilities have produced nuclear weapons, provided nuclear fuel materials for power reactors, and conducted a wide spectrum of research related to nuclear safety and other scientific issues. While completing this work, many of the employees have been exposed to ionizing radiation and other potentially hazardous materials.

Since 1991, the National Institute for Occupational Safety and Health (NIOSH) has conducted analytical epidemiologic studies of workers at DOE nuclear facilities, through a Memorandum of Understanding between the DOE and the U.S. Department of Health and Human Services (DHHS). The agreement occurred in response to recommendations to the Secretary of Energy in 1989 by the independent Secretarial Panel for the Evaluation of Epidemiologic Research Activities (SPEERA).

This technical report, entitled *A Nested Case-Control Study of Leukemia and Ionizing Radiation at the Portsmouth Naval Shipyard*, is one several products of the NIOSH Occupational Energy Research Program that are being published as a series. Most of these studies include detailed historical exposure assessments for radiation and other potentially hazardous agents so the health risks at different levels of exposure can be accurately estimated. Each of these studies contributes to the knowledge required to ensure that workers are adequately protected from chronic disease over their working lifetimes.

Distribution of this final report addresses the recommendation of the SPEERA panel to make reports of study results more readily available to workers and the interested public. Additional information about the NIOSH epidemiologic research program of occupational health studies involving the DOE nuclear weapons workforce may be obtained by contacting NIOSH toll free at 1-800-35-NIOSH (1-800-356-4674) or by visiting the NIOSH website for the Occupational Energy Research Program at <http://www.cdc.gov/niosh/2001-133.html>

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Ms. Barbara Bauman and Ms. Sondra Wisdom of the National Public Record Center facility provided invaluable assistance locating critical medical record files, enabling an analysis of work-related medical X-ray exposure.

Current and former staff at DOE headquarters, including Marsha Lawn, Gerry Petersen, and Heather Stockwell, provided ongoing encouragement for completion of the study.

Former NIOSH scientists Robert Rinsky, William Murray, and Tim Jiggins carried out initial epidemiological, health physics, and industrial hygiene work on the study. We are grateful to the many current and former government and contract staff working with NIOSH who have provided essential services for the collection, compilation, and validation of records and data used in this study. These include Dennis Zaebst, David Back, Kevin Hubbard, Dianne Reeder, Melissa Tolson, Kim Collins, Susan Freking, and Donna Pfirman, who was instrumental in the preparation of this report.

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Finally, Drs. Buncher, Lockey, Rice, Rinsky, and Spitz from the Department of Environmental Health at the University of Cincinnati provided invaluable review, advice, and guidance to the study team.

Abstract

Objective

To determine if there is an association between occupational exposure to external ionizing radiation and leukemia mortality among civilian Portsmouth Naval Shipyard workers after potential confounders and effect modifiers such as solvent exposure, and time since exposure are considered.

Methods

This study employs a nested case-control design and includes 115 leukemia cases and 460 controls. Among the cases and controls, 201 (35%) were monitored for radiation exposure. Badge doses and exposures to work-required medical x-rays were included in the analysis. Benzene and carbon tetrachloride exposure was assessed using workers' job information and industrial hygiene records. Conditional logistic regression was used to analyze the exposure-response relationship between external ionizing radiation exposure and leukemia mortality.

Results

A significant positive association was found between leukemia mortality and external ionizing whole-body radiation exposure (OR= 1.08 at 10 mSv; 95% CI=1.01, 1.16) adjusting for gender, radiation worker status and solvent exposure duration. The latter factor (OR= 1.03 at one year of exposure; 95% CI=1.01, 1.06) was also significantly associated with leukemia mortality. The incorporation of estimated doses from work-related medical x-ray exposures did not change the leukemia risk estimate.

Significantly different exposure-response trends were observed in the 2.5 – 5 years since last exposure category compared to the > 10 years since last exposure category. The choice of categories for time since last (radiation) exposure (TSLE) classification did not greatly alter these findings.

In this study the results using a linear ERR model estimate an excess relative risk of 23% (95% CI = 3%, 88%) per 10 mSv of external radiation exposure from occupational sources after potential confounders were considered in the analysis. The excess relative risk has previously been estimated at between -4.1% and 19.0% at 10 mSv in other epidemiologic studies of workers exposed to penetrating ionizing radiation (Fraser et al., 1993) and approximately 4% for individuals in the Japanese Life Span Study who were simultaneously exposed at various ages and developed diseases at different times after exposure (BEIR V, 1990; Schubauer-Berigan and Wenzl, 2001).

Conclusion

We observed a positive association between leukemia mortality and increasing external whole-body ionizing radiation exposure, adjusting for radiation worker status and solvent exposure duration. A significant exposure response between leukemia mortality and the duration of time workers were employed in job categories where solvent exposures were probable was also observed. However, solvent exposure was not a confounder of the association between radiation exposure and leukemia risk.

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1. Introduction

1.1. Study Purpose

This is a nested case-control study investigating associations between external ionizing radiation exposure and leukemia mortality among civilian workers employed for at least one day between January 1, 1952 and December 31, 1992 at the Portsmouth Naval Shipyard (PNS). The nested case-control study design offers the opportunity for a more in-depth examination of exposures from solvents (particularly benzene and carbon tetrachloride) and work-related medical x-rays and their relation to leukemia risk than has been possible in previous cohort mortality studies of PNS workers.

No previous PNS studies have been able to assess solvent exposure as a confounder or effect modifier because coded work history information was not available for non-radiation-monitored workers. Because the case-control study design allows for increased efficiency in the collection of information, it was feasible to code detailed work history information for all cases and controls and include this information in the analysis. The work histories identified the job and shop assignments for all the study subjects throughout their work history at PNS. Using industrial hygiene information from the shipyard with the coded work history information, it was possible to develop a qualitative chemical exposure assessment based on job and shop combinations that were most likely to have workers exposed to solvents (primarily benzene and carbon-tetrachloride). Employment duration in these exposed jobs and shops was used to estimate magnitude of cumulative exposure.

NIOSH research published in 2002 suggests that work-related medical x-ray exposures can add substantially to a worker's cumulative occupational dose and should be considered when estimating the effects from low-level radiation exposures (Cardarelli, 2002). No previous studies of PNS workers examining the effects of external ionizing radiation exposure have assessed the impact of work-related medical chest x-ray exposures on a worker's cumulative exposure. Because of the availability of the worker medical records containing information about the number and type of work-related medical x-rays for PNS civilian employees, this study provides a unique opportunity to account for this additional source of exposure to ionizing radiation.

1.2. Specific Aims

This study has three specific aims:

1. To conduct a nested case-control study that investigates the relationship between the dose from external occupational radiation exposure and leukemia mortality.
2. To utilize uniquely available radiation dosimetry and medical records to estimate dose from occupational sources and work-related medical x-rays.

3. To conduct a dose response analysis to detect any relationship that might be present.

2. Study Relevance

Previous studies of PNS workers did not include exposure to work-related medical x-rays as one of the sources of external occupational ionizing radiation exposure, making it possible that doses for some workers were underestimated. This study will provide an opportunity to study the effects of chronic low-dose external radiation exposures, including doses resulting from work-related medical x-rays.

The proposed study includes a population of workers whose primary exposure is likely to have been external ionizing radiation. There are relatively complete and accurate dosimetry and work-related medical x-ray exposure data available for each worker and there has been sufficient length of follow-up to study mortality from cancers, such as leukemia, that have relatively short latency and morbidity periods. This research study, because it utilizes a nested case-control design, offers an opportunity to provide less biased results than those derived from the full PNS cohort analysis.

3. Study Design and Methods

This section describes the type of work performed by civilian workers at PNS, summarizes results of previous occupational studies and the choice of exposure measurements, temporal, and demographic variables used in this new analysis. Sources of occupational radiation exposure and the methods used at the shipyard to monitor and record radiation and chemical exposures are also described. Finally, the analytical and statistical methods used in the analysis are discussed.

3.1. Brief History of the Portsmouth Naval Shipyard

The Portsmouth Naval Shipyard (PNS) was established in 1800 as a United States Naval Facility and has been involved in the design, construction, and repair of all types of warships, from those powered by sail to nuclear-powered submarines. PNS built what has been called the first United States submarine, the L-8, which was commissioned in 1917, and established the record for building the greatest number of submarines during a calendar year—31 in 1944. From 1917 to 1971, the shipyard constructed a total of 137 submarines (McDonough, 1978).

In 1950, PNS instituted a radiation dosimetry program to monitor primarily industrial radiographers and individuals responsible for the calibration of various types of x-ray machines. The shipyard Radiological Health Branch was established within the existing shipyard medical department in 1955 with the initiation of employee training to overhaul and construct nuclear powered submarines. From 1955 to 1971, a fleet of 100 nuclear-powered submarines was constructed by Portsmouth and Mare Island (California) Naval shipyards and three private shipyards. Ten of these submarines were constructed at the Portsmouth Naval shipyard. The PNS constructed the USS Swordfish, which was commissioned on September 15, 1958, and was the

first nuclear submarine built in a United States Government shipyard. The nuclear-powered USS Sand Lance (SSN 660), commissioned on September 25, 1971, was the last submarine built at the PNS (McDonough, 1978).

In the late 1950s and early 1960s, as more nuclear-powered submarines entered the U.S. naval fleet, the need for shipyards to overhaul and maintain nuclear submarines increased. In June 1959, PNS began its first overhaul, repair, and refueling of a nuclear submarine, the USS Nautilus. From 1959 through 2002, the shipyard performed 221 nuclear-powered submarine overhauls, repairs, and refuelings (Appendix D).

The Portsmouth Naval Shipyard is a large industrial complex employing workers from a variety of trades including welding, insulating, electronics, woodworking, foundry, rubber working, pipefitting, painting, engineering, rigging, steel fabrication, and machining. Potential sources of ionizing radiation exposure include activated cobalt-60 in the stainless steel tubing used in the nuclear reactor cooling system and industrial radiography and medical surveillance involving x-rays. PNS workers were also potentially exposed to organic solvents including benzene and carbon tetrachloride (Stern et al., 1986). Historically, the number of civilian workers employed at the shipyard has increased dramatically during times of war, such as in 1918, when civilian employment was 5,500; in 1943, when civilian employment was 20,466; and in 1952 during the cold war and Korean conflict, when civilian employment reached 10,559. Currently there are 4,083 civilian workers employed at PNS (Appendix C).

3.1.1. Previous occupational studies conducted at PNS

In 1978, Najarian and Colton reported the results of a proportional mortality ratio analysis of workers hired during 1959 through 1977 at PNS. The study was conducted after Najarian treated a 63-year-old former PNS employee with hairy-cell leukemia who reported that he knew of several younger nuclear workers at the facility who had died of leukemia. Najarian and Colton reported a five-fold increase in proportional mortality due to leukemia and a two-fold increase in mortality due to all cancers combined among workers exposed to low levels of ionizing radiation at PNS. No increased mortality for leukemia was observed for PNS workers not monitored for ionizing radiation (Najarian and Colton, 1978).

In response to the findings reported by Najarian and Colton, The United States Congressional Subcommittee on Health and the Environment held public hearings to discuss workplace safety at PNS. A primary request from the committee was that the National Institute for Occupational Safety and Health (NIOSH) conduct a study to further evaluate the reported excess risk of leukemia. NIOSH responded by conducting a cohort mortality study that included 24,545 PNS civilian workers (white males only) employed from January 1, 1952, through August 15, 1977. The primary exposure examined in the study was external ionizing radiation. The cohort was divided into three subcohorts based on radiation exposure: Subcohort I included 7,615 workers who had a recorded lifetime cumulative radiation exposure history of at least 0.001 rem.

Subcohort II included 15,585 workers who were never assigned work involving occupational exposure to radiation. Subcohort III included 1,345 workers who were monitored for radiation exposure but whose total lifetime cumulative dose was recorded as 0.000 rem (Rinsky et al., 1981).

In 1981, NIOSH published the results of the mortality study (Rinsky et al., 1981), which, unlike the Najarian and Colton study, reported no increase in leukemia or overall cancer mortality. The standardized mortality rate (SMR) for leukemia among the radiation-exposed workers with at least 0.001 rem of lifetime cumulative dose (Subcohort I) was 0.84 (95% CI 0.34, 1.74). The SMR for leukemia among the non-radiation workers (Subcohort II) was 1.06 (95% CI 0.72, 1.51) (Rinsky et al., 1981).

In 1985, NIOSH conducted a leukemia case-control study of PNS workers including all white male PNS civilian workers ever employed between January 1, 1952 and December 31, 1980. The study, which included 53 leukemia cases, revealed no statistically significant positive association between leukemia and exposure to external radiation or possible exposure to organic solvents, which could have included benzene, xylene, toluene, and carbon tetrachloride. However, elevated leukemia risk was seen in workers with a total recorded cumulative external ionizing radiation exposure of least 1 rem, with no lagging of exposure assignment (Stern et al., 1986).

In 2003, a NIOSH analysis of mortality of an expanded PNS cohort was completed (Silver et al., 2004). The updated mortality study population includes 37,853 male and female workers hired before January 1, 1993 with vital status follow-up through 1996. In the full cohort, leukemia mortality was as expected based on U.S. population rates (SMR = 1.01, 95% CI = 0.84, 1.22). The SMR showed a non-statistically significant elevation among non-radiation-monitored workers (SMR = 1.08, 95% CI = 0.86, 1.35), and for radiation exposed workers the SMR was below expectation. However, dose-response analysis revealed a non-statistically significant elevation in leukemia mortality among radiation workers who had an exposure between 1 – 9.9 mSv (Standardized Rate Ratio [SRR] = 2.06, 95% CI = 0.77, 5.50) when compared to workers in the baseline group (0 – 0.9 mSv) and statistically significant increases among workers receiving an exposure between 10 – 49.9 mSv (SRR = 2.94, 95% CI = 1.10, 7.86) and greater than or equal to 50 mSv (SRR = 5.08, 95% CI = 1.35, 19.20) (Silver et al., 2004). No evaluation of potential confounding by solvent exposure was conducted.

3.2. Study Design—Leukemia Case-Control Study

This study employed a nested case-control design to analyze the association between occupational external ionizing radiation exposure and leukemia, while controlling for confounding and evaluating effect modifiers. The study population from which the cases and controls were selected has been described in the NIOSH cohort mortality study of civilian workers employed at the Portsmouth Naval Shipyard (Silver et al., 2004), and consists of 37,853 civilian workers employed between 1/1/52 and 12/31/92 whose vital status and cause of death were obtained through 12/31/96. At the end of vital status follow-up (12/31/96), approximately

two-thirds (25,460) of the workers in the study population were classified as alive and one-third (12,393) as deceased. Personal radiation monitoring was conducted for personnel meeting the training and physical requirements (i.e. radiation qualified workers) required to enter designated radiological areas. There were 13,468 workers in the total cohort of 37,853 that were monitored for external ionizing radiation. Of these 13,468 radiation-monitored workers 11,791 (88%) had a recorded exposure greater than zero and 1,677 (12%) had a recorded exposure of zero.

3.3. Vital Status Ascertainment

The vital status of the PNS cohort of 37,853 from which the cases and controls were selected was determined through December 31, 1996. For the cohort of workers employed through August 15, 1977, vital status through that date was assessed by active follow-up and death certificates obtained from the states. Members of the cohort who were not known to be deceased were submitted to the National Death Index (NDI) service of the National Center for Health Statistics. NDI Plus returns coded causes for deaths occurring in 1979 or later. The full cohort was also submitted to the Social Security Administration for a “presumed living” search. This search provides date-of-death information both before and after 1979, and also confirms alive status for those paying social security taxes or receiving social security benefits. It does not provide the cause of death for deceased individuals, nor does it identify individuals who are not actively paying into or receiving Social Security benefits. Death certificates were sought from the state in which death occurred for all persons who were determined to be dead from the SSA results, but who had not been found on the NDI search. The certificates were coded by a qualified nosologist to the ICD (International Classification of Diseases) revision in effect at time of death, for consistency with the 1981 PNS mortality study by Rinsky et al. (Silver et al., 2004).

3.4. Method of Case and Control Selection

3.4.1. Selection of cases

All leukemia deaths that occurred between 1/1/52 and 12/31/96 among the entire PNS cohort of 37,853 civilian workers were selected as cases. All of the leukemia cases have an underlying cause of death classified to leukemia under the revision of the International Classification of Diseases in effect at the time of death (Table 3.8.1).

3.4.2. Selection of controls

For each case, risk sets were defined from the entire cohort of PNS civilian workers first employed between 1/1/52 and 12/31/92 (Beaumont et al., 1989; Checkoway et al., 1989). Four controls per case were randomly selected from each risk set. Selection was done by a computer program developed by NIOSH to perform incidence density sampling of potential controls for nested case-control studies (Beaumont et al., 1989). The program considers each case and selects controls from the cohort who are at risk of an observed failure (dying from leukemia) at the time the case fails (dies from leukemia). The risk set is made up of all controls who were under observation and who lived to an age equal to or greater than the age of the index case at the time

of failure. Time is defined as the length of life (attained age) of the case; the cases and controls are matched on attained age because it is a strong predictor of leukemia mortality and therefore an important potential confounder of the associations of interest in these analyses.

To illustrate how controls were selected, consider a PNS worker who dies of leukemia at age 62. Potential controls were all PNS workers who were “at risk” [workers who were employed by PNS at or earlier than age 62 and were still alive at age 62]. A control’s exposure was considered only up to the age at which the corresponding case died.

A power curve was developed based on the following assumptions: 1) that 40% of the cases and controls were monitored for external ionizing radiation; 2) an alpha level of 0.05 using a two-tailed test; 3) a power of 0.80. A ratio of four controls to each case was found to provide power of 45% for detection of an odds ratio of 1.9 at 150 mSv (Appendix I) (Egret-Siz, 1997). Power was increased very little with the addition of more controls per case (i.e., power is case-limited).

3.5. Description of the Primary Radiological and Chemical PNS Exposures

3.5.1. Overview of PNS work organization

All PNS employees are assigned to trade-specific occupational groups called shops, and each shop is responsible for specific tasks in submarine construction, overhaul, refueling, or in general support of the shipyard. All workers within each shop are assigned job titles that further describe their specific functions. Personnel records kept by the shipyard document all job and shop assignments with dates for all workers throughout their working careers at the shipyard (Rinsky et al., 1981).

In addition to shop and job designations, workers who were “radiation-qualified” are also identified in the shipyard records. Since the establishment of the film dosimetry program on July 1, 1950, workers who have been selected and trained for work in radiation-controlled areas on the basis of their expertise in a particular trade have been radiation-qualified and a record of their dosimetry established and retained. Unlike chemical exposures, for which there are few records directly describing the types and extent of individual exposure, individual radiation-monitoring records were maintained for all qualified radiation workers at the shipyard (Daniels et al., 2004a; Murray and Terpilak, 1983; PNS Report RC-105-1, 1980).

3.5.2. Radiation exposure during overhaul, repair, and refueling activities

The propulsion plants of nuclear-powered submarines primarily use highly purified water to generate steam for propulsion and auxiliary machinery. These propulsion plants are closed-loop pressurized heat transfer systems with a primary system that includes the nuclear reactor, pumps to re-circulate cooling water in pipes through the reactor, and steam generators. Steam generators transfer heat from the primary system to a secondary system that drives turbine generators to

supply the ship with electricity and for propulsion. Both the primary and secondary systems are closed-loop systems, meaning that the water is re-circulated and either stays inside the core or outside the core. The nuclear reactor core, primary coolant pipes, and steam generators are located in a shielded compartment that is not accessible during operation (Federation of American Scientists, 2000).

Trace amounts of impurities are formed from the corrosion of surfaces of metal pipes used in the primary coolant system and steam generators. Some of the impurities eventually become suspended in the circulating coolant, and enter the reactor core where they become radioactive by neutron activation. [Activation is the process by which the nucleus of a non-radioactive substance becomes radioactive after absorbing one of the neutrons produced in the fission of nuclear fuel in the reactor (Borders, 1991)]. Much of the activated corrosion products in the coolant are removed by the water purification system; however, some of the activation products are created within the walls of stainless steel pipes throughout the primary coolant system, steam generator, and other parts of the reactor. Exposures to radiation emitted from these activation products occur primarily during maintenance, repair, and refueling operations, when workers enter the reactor compartment (Rice and Kindley, 1980; Murray and Terpilak, 1983; Daniels et al., 2004a). According to shipyard radiological personnel (Brann, 1998), approximately 95% of the total radiation dose to the entire PNS cohort is from external exposure to radiation emitted by activation products.

Within 24 hours following reactor shutdown, the long-lived activated corrosion products become the dominant source of radiation exposure, and typically more than 50% of total activity deposited in the reactor system pipes results from the long-lived cobalt-60, which has a half-life of 5.3 years. Other radionuclides and their half-lives include: nickel-63 (100.1 years), manganese-54 (312.3 days), and chromium-51 (27.7 days) (Murray and Terpilak, 1983).

3.5.3. Radiation exposure from fission products

The enriched uranium nuclear fuel is clad with a zirconium metal alloy to retain virtually all of the fission products including gaseous radioisotopes such as Krypton-85, Xenon-133, and Iodine-131 (Murray and Terpilak, 1983). The fuel is installed in the reactor core that is sealed inside a thick-wall pressure vessel that provides additional shielding from radiation associated with fission and activated corrosion products. This design is the primary reason that exposures from fission products are low during operation of the submarine. Work near the reactor in the first few weeks following shutdown may result in some radiation exposure from high-energy fission products remaining in the reactor core; however, this exposure is estimated to be less than 5% of the total cumulative shipyard dose (Daniels et al., 2004a).

3.5.4. Neutron exposure

Significant neutron exposure is possible only during reactor operations, when access to the reactor compartment is prohibited. Therefore, occupational exposure to neutrons is confined to

personnel who were on-board during power operations (e.g., special testing, sea trials) or worked with neutron calibration sources. Only twelve of the 575 cases and controls in this study had recorded neutron exposure. The mean exposure for these 12 workers was 0.16 mSv, the median was 0.15 mSv, and the maximum recorded exposure for one worker was 0.44 mSv. The exposure of 0.44 mSv accounted for only 0.29 percent of the worker’s cumulative occupational exposure. The cumulative neutron exposure for the 12 workers accounted for 0.04 percent of the cumulative occupational exposure recorded for all cases and controls. Because of the small amount of the total occupational exposure due to neutrons and the small number of workers exposed, neutron exposure was not included in the analysis.

3.5.5. Internal radiation exposure

While external radiation exposure, particularly during overhaul, repair, and refueling activities, is the primary type of shipyard exposure, internal exposure to ionizing radiation has been recorded by the shipyard radiological department. Internal exposures occurred when parts of the reactor system were cut open during overhaul or maintenance activities and primarily involved machinists and radiation technicians. However, none of the 575 cases and controls had any records of detectable internal radiation exposure.

3.5.6. Work-related medical x-ray exposure

PNS workers were also exposed to external ionizing radiation as a result of work-related medical x-rays that were performed as part of the shipyard occupational medical monitoring programs. Work-related medical x-ray examinations are defined as those x-ray examinations performed at PNS as a condition of shipyard employment such as; annual radiation qualification examinations, pre-employment screening, separation and/or disability physical examinations, and mass tuberculosis screening performed in 1948, 1951, 1952, and 1956. For this study, NIOSH researchers located and reviewed all of the available medical records for each of the cases and controls for medical x-ray information. A total of 3,162 records of actual medical x-ray examinations were performed at PNS between 1941 and 1995. This represented 511 cases (89%) of the 575 cases and controls identified and extracted from the physical examination records. It was determined that 2,449 (77%) of the x-ray examinations were work-related and 713 (23%) were non-work-related. Of the work-related medical x-rays, 2,444 (99.8%) were of the chest and five were of the lumbar-sacral spine (Table 3.5.6).

Body Location	Frequency	Percent	Cumulative Frequency
Chest	2444	99.80	2444
Lumbar-Sacral Spine	5	0.20	2449

Non-work-related medical x-ray examinations are defined as those x-ray examinations performed due to an injury or illness or as follow-up to a work-related x-ray procedure. Because it was not clear from the medical

records if the non-work-related examinations were the result of a job related illness or injury, they were separated from the work-related examinations for the analysis. Of the 713 non-work-related x-rays, 196 (28%) were chest x-rays (Appendix E).

3.5.7. Types of chest x-ray techniques used at PNS

For this study, chest x-ray techniques were categorized as photofluorographic or direct radiographic. When the direct radiographic x-ray technique is employed, the x-ray film is directly exposed by the x-rays passing through the chest. The photofluorographic technique is a method in which a fluorescent screen placed next to the patients' chest produces an image of the internal structure of the chest. This image is then photographed, providing a miniature x-ray image similar to the large picture obtained in direct radiography. Photofluorography was used when large numbers of individuals needed exams because it was less expensive than direct radiography. However, radiation exposures from the photofluorographic technique are much greater than those received from direct radiographic techniques (Daniels et al., 2004b).

The PNS medical records indicate that photofluorographic techniques using either 70 mm film or 35 mm film were used for nearly all work-related chest x-ray examinations conducted at PNS prior to May 1966. Of the 2,444 work-related chest x-ray examinations given to the cases and controls, 1,578 (65%) used photofluorographic techniques.

All photofluorographic exams are assumed to be single exposure posterior-anterior (PA) views of the chest. There is no evidence in the records that stereographic imagery was used in conjunction with photofluorographic equipment. In instances where abnormal results were indicated by a photofluorographic image, the PNS medical records indicate that a retake was performed using the direct radiographic technique. Available medical records indicate that non-work-related chest x-ray examinations also used the direct radiographic technique. Therefore, in this study all retakes and non-work-related chest examinations are assumed to employ direct radiographic techniques only (Daniels et al., 2004b).

Because medical records were not available for 48 (9%) of the 551 cases and controls with work-related medical x-ray exposure, the following assumptions were adopted from the information that was available for the 503 cases and controls with records (Daniels et al., 2004b). These assumptions were used to estimate x-ray doses for the 48 workers who had no medical x-ray records.

- All work-related medical x-rays were a single (PA) view of the chest, and that there was 1.5 mSv of dose for each chest x-ray using photofluorographic techniques and 0.04 mSv for each chest x-ray using direct radiography techniques.

- All routine x-ray examinations performed prior to 5/1/1966 used photofluorographic techniques. After May 1966, all work-related chest x-ray examinations were assumed to have been produced by direct radiography techniques.
- All workers hired between 1/1/1948 and 12/31/1956 received one pre-employment medical examination (during the year hired) that included a chest x-ray.
- Radiation-qualified workers who worked between 1/1/1958 and 12/31/1962 received one baseline medical examination that included a chest x-ray.
- Radiation workers employed between 1/1/1963 and 12/31/1968 received a medical examination that included a chest x-ray each year that at least one occupational dose is recorded.
- Any person employed in 1948, 1951, 1952, and/or 1956 received an annual photofluorographic chest examination for mass tuberculosis screening (Daniels et al., 2004b). The frequency of work-related and non-work-related x-ray examinations by examination type is shown in Appendix F.

3.5.8. Method for estimating dose equivalent to the active bone marrow from occupational work-related medical x-rays

Estimates of the bone marrow absorbed dose from x-ray exposure for PNS workers was obtained by mathematical modeling of x-ray photon interactions in tissue using a Monte Carlo simulation program developed by the Finnish Center for Radiation and Nuclear Safety. The program input parameters included information about the PNS x-ray procedures and equipment, exposure geometry, and photon energies (Daniels et al., 2004b). The bone marrow was chosen as the target organ because it is the malignant transformation of cells in this organ that possibly cause leukemia, and it is believed that the probability of such malignant transformation is related to the dose delivered to the organ. (UNSCEAR, 2000; Jorde, 1999; Mitus & Rosenthal, 1995).

A radiation weighting factor of unity is assumed to convert absorbed dose (mGy) to dose equivalent (mSv) (ICRP, 1974). Dose conversion factors were calculated using the methods described by the ICRP Publication 74 to estimate doses to the active bone marrow from results of occupational whole-body external radiation exposure measured using the personal dosimeter for all cases and controls (International Commission on Radiological Protection [ICRP], 1974). These dose conversion factors accommodated differences in dosimeter calibration, spatial response, and incident photon energies at the PNS that occur over time (Daniels et al., 2004b).

It is important to note that, other than using individual dosimetry results and limited x-ray examination data, bone marrow dose estimates were not performed on an individual basis. Rather, many generalizations were required to develop the dose conversion factors that were

applied to the study group as a whole. Large uncertainties exist in estimating a particular worker's bone marrow dose, given the variability of several critical parameters over the period of the study. These parameters include but are not limited to x-ray procedures and equipment, exposure geometry, incident photon energies, and worker age, sex and anatomy (Daniels et al., 2004b).

3.6. Radiation Exposure Assessment

3.6.1. Devices used to monitor external ionizing radiation exposure at PNS

Monitoring of external radiation exposure began in the summer of 1950 with the introduction of a film badge program for industrial radiography personnel, and expanded in 1958 with the beginning of the naval nuclear propulsion program. The detection threshold for gamma radiation for the film badge prior to 1957 is reported to be 0.2 mSv per monitoring period (Brann 1998). Design improvements in the film badge made in 1969 reduced the detection threshold for gamma radiation to 0.1 mSv per monitoring period (Brann, 1998; Daniels et al., 2004a). Film badges were used until October 1974, when the calcium fluoride thermoluminescent dosimeter (TLD) was introduced as the official monitor for PNS personnel. The minimum detection level of the TLD is reported by the shipyard to be 0.01 mSv (Brann, 1998). The calcium fluoride TLD continues to be the primary personal dosimeter for the shipyard (Daniels et al., 2004a). Badge readings were recorded bi-weekly through 1959 and monthly after 1960 by PNS. Cumulative external radiation exposure was calculated for each case and control by summing all of the recorded dosimeter badge results.

3.6.2. Evaluation of missed radiation exposure due to the sensitivity of dosimetry devices

The combination of the limited sensitivity of the personal radiation dosimeter and greater dosimeter exchange frequency can lead to underestimation of occupational radiation exposure in very low dose-rate work environments. Dosimeters worn for longer periods of time could more readily detect low dose-rate exposures (Strom, 1986). The methods used to estimate the missed exposures for the cases and controls with at least one recorded exposure of zero prior to the introduction of TLDs in 1974 are described by Daniels et al. (2004b).

3.6.3. Evaluation of occupational radiation exposures that have occurred while workers were previously employed at a facility other than PNS

The shipyard kept records of radiation exposures that radiation-qualified workers received prior to their beginning work at PNS. These workers received radiation exposure while employees of the Department of Defense (Army, Air Force, Navy, and Marines), the Department of Energy, and commercial nuclear companies. Some of the workers received prior exposure while employed as medical support staff (e.g., x-ray technicians and radiologists), or because of participation in atomic weapons testing. Three individuals in the study reported offsite radiation

exposure prior to beginning work at PNS. Actual exposure data from the previous employer was available for two of the individuals. For the third individual, NIOSH health-physics staff calculated a yearly exposure estimate using National Council on Radiation Protection (NCRP Report No. 101) for Department of Defense personnel. None of the offsite exposure recorded by the three individuals was the result of nuclear weapons testing (Daniels et al., 2004a).

3.6.4. PNS methods of recording external ionizing radiation exposure

Radiation-monitoring film badges were processed every two weeks prior to 1960, and monthly after 1960. All individual badge results were entered monthly onto the form DD 1141, *Record of Occupational Exposure to Ionizing Radiation*, which became the official dose of record for the monitored individual. The DD 1141 record contains the worker's name, social security number, date of employment, and monthly and life-time cumulative radiation exposure information. The cumulative onsite badge exposure variable used in the study analysis is based on radiation monitoring results recorded by PNS dosimetry on the form DD 1141, as the sum of gamma (penetrating), x-ray, and neutron results for each monitoring interval.

3.7. Chemical exposures assessment

3.7.1. Overview

Shipyards jobs have always included insulating, pipefitting, mechanical repair and maintenance, electrical and instrument work, rigging, welding, painting, chipping, caulking, abrasive blasting, and metal work. These jobs were performed on both moored and dry-docked submarines and in buildings housing various shops on the shipyard. Work performed on-board the submarines is frequently done in confined spaces that require ventilation which, if not performed properly, can fail to adequately control chemical exposures. Also, because of the confined work environment, indirect exposures can occur from contaminants generated by adjacent workers performing different tasks as well as direct exposures from contaminants generated by the individual task being performed. These cross-contaminating exposures were likely to be more frequent on-board the submarines than in other locations in the shipyard because unlike some of the shop areas on land it was not possible to segregate work areas by job type on the submarine.

3.7.2. PNS industrial hygiene program

The PNS medical clinic and, beginning in the early 1980s, the industrial hygiene (IH) department kept records providing information about some types and amounts of chemical and material products used during construction, overhaul, and maintenance activities. This information includes various manufacturing process descriptions, production flow charts, plant production inventories, and routine inspection and accident reports. The IH department also kept records of the results of environmental monitoring that was conducted to detect the presence of airborne contaminants within the shipyard complex.

Additional information useful for the evaluation of chemical exposures kept by the shipyard IH department includes records detailing work practices and process improvements. The work practice records describe the use of personal protective equipment during sand blasting, welding and painting activities, and local exhaust ventilation used while working in confined spaces. The shipyard reduced potential exposures by replacing toxic chemicals with less toxic substitutes when possible. For example, in 1948 the shipyard began phasing out the use of the solvent carbon tetrachloride (Appendix G). Also, the shipyard substantially decreased the use of benzene by discontinuing the purchase of 100% benzene by February of 1958 (Appendix G); however, it remained as a contaminant in petroleum distillates (2 - 5%) such as gasoline and in some solvents (11 -15%) such as toluene, xylene, and naphthas. Records detailing new construction, refueling, and overhaul at the shipyard were also kept by the IH and Public Affairs offices. These records identify specific periods of time during which either significant increases or decreases in work activity occurred at the shipyard (Appendices B and C). For example, following World War II and until 1958, few diesel submarines were constructed and, because of this decline in activity, exposure frequency and duration to various chemicals (benzene in petrol distillates and diesel fuel) and aerosols were probably somewhat lower in those years than during the World War II period. In the late 1950s and through the 1960s, both new construction and overhaul increased significantly, which probably increased the frequency and duration of these exposures.

3.7.3. Identification of jobs and shops with the greatest potential exposure to benzene and carbon tetrachloride

Documents from the shipyard and NIOSH industrial hygiene surveys of 17 PNS shops conducted in 1979 and 1980 were reviewed to determine which jobs and shops had the greatest potential for benzene, and carbon tetrachloride. These documents provided information such as functional descriptions of various shops, manufacturing process descriptions, production flow charts, plant production inventories, inspection and accident reports, work practice and process improvements, occupational illness reports, and organizational charts. Limited sample data were available confirming exposure to the chemicals/chemical families listed by shop in Table 3.7.3. For example, the woodworking employees used benzene and carbon tetrachloride for cleaning tasks and were often assigned to shops where rubber manufacturing processes that tend to use larger quantities of solvents were located. Welders used carbon tetrachloride for multiple tasks and petroleum distillates containing benzene were present in the transportation shop. Solvents which contained benzene, toluene, and xylene (BTX) and carbon tetrachloride were used by employees in the painting shop (Table 3.7.3).

Table 3.7.3. Job/Shops Solvent Exposures—Including Benzene and Carbon Tetrachloride	
Transportation	
Total Chlorinated Hydrocarbons	Benzene
Trichlorotrifluoroethane	Carbon Tetrachloride
Trichloroethylene	
Welding	
Total Chlorinated Hydrocarbons	Carbon Tetrachloride
Naphthas	
Machining	
Trichloroethylene	Acetone
Trichlorotrifluoroethane	Petroleum distillates
Machining Oils	
Electrical	
Toluene Diisocyanate	4,4'-Methylenebis (2-chloroaniline) (MBOCA)
Naphtha	Carbon Tetrachloride
Woodworking	
Butyl Alcohol	Trimellitic Anhydride
Toluene Diisocyanate	Amines
Benzene	Monostyrene
Toluene	Methylene Chloride
Vinyl Chloride	Hydrogen Chloride
Aromatic Hydrocarbon	Hydrogen Sulfide
Ethyl Alcohol	Isopropyl Alcohol
	Petroleum Distillates
Painting	
Xylene	
BTX (Benzene/Toluene/Xylene)	Isophorone
Butyl Alcohol	Ethanol
Toluene	Epichlorohydrin
Acetone	Cyclohexanone
Methyl Ethyl Ketone (MEK)	2-Butoxyethanol
Isobutanol	Monoethanolamine
2-Ethoxyethanol	Methyl Isobutyl Ketone
n-Butyl Glycidyl Ether	Carbon Tetrachloride

A precise estimation of job-specific solvent exposures is complicated and difficult to achieve because of two main characteristics of the work performed at the shipyard. First, much of the work occurred in enclosed spaces designed to be air and watertight; workers of different occupational trades typically must work side-by-side in such spaces, each contributing to the others' exposures. Second, while an employee is usually assigned to a single shop, primarily for pay purposes, individual day-to-day work assignments can and often do vary considerably. For example, an individual assigned to a shop may be given either shipboard or non-shipboard tasks to perform and may also perform tasks in a different shop. Both of these characteristics can contribute to variability in the types and magnitude of exposures associated with any particular job. Due to the variability of day-to-day work assignments and the limited availability of shop and job specific industrial hygiene monitoring data for potential leukemogens, a qualitative chemical exposure assessment was developed based on the duration of employment in jobs and shops and time periods when exposure to solvents such as benzene and carbon tetrachloride were most likely to have occurred.

3.7.4. Identification of job and shop assignments for cases and controls

Job and shop assignments for each case and control throughout their employment at PNS were identified. This detailed job history information was collected from the United States Navy Standard Form 7 (SF-7) work history record. Each SF-7 work history record contained the worker's name, social security number, and the beginning and ending dates of employment. Any change in shop or job assignment and the date of each new assignment was recorded in the SF-7 according to standard operating procedure for each case and control. In addition, each job title and shop assignment was used by NIOSH to generate a four-digit code number—the first two digits identified the shop assignment and the last two the job title for each worker. A total of 1,372 job title and shop combinations were abstracted from the SF-7 for the study subjects.

3.7.5. Standardization and grouping of job titles

Variations and abbreviations of job titles from the shipyard records were standardized. Next, exposure potentials were grouped into several categories based on job titles and shops. Shops were grouped by: 1) function of the shop (i.e., production, administrative, support, etc.); 2) types of chemicals and materials utilized; and 3) whether employees assigned to the shop were responsible for performing work on-board submarines. The job titles were grouped by: 1) type of work tasks performed, and 2) type of potential chemical exposures.

The following examples illustrate the process followed to group job titles within a shop. First, consider the following job titles: Painter, Painter-helper, and Painter-apprentice. These job titles were all collapsed into the same job title—Painter—because they have the same or very similar benzene and carbon tetrachloride exposure potential and perform the same or very similar tasks throughout the study period. Therefore, three job titles are collapsed into one. Next the assigned shop was taken into account to determine each Painter's benzene and carbon tetrachloride exposure potential. For example, a painter assigned to a production paint shop that performs

work on-board submarines and across the shipyard is thought to have benzene and carbon tetrachloride exposure potential and is assigned to the exposed category. However, a painter assigned to a Planning and Estimating Shop, which is an administrative shop that performs planning tasks primarily in an office setting, is thought to have little benzene and carbon tetrachloride exposure potential and is therefore assigned to the non-exposed category (Appendix H, Table 1). A final review of the job shop collapse was conducted by NIOSH and shipyard Industrial Hygiene staff.

3.7.6. Analysis of benzene and carbon tetrachloride exposure

Because of limited chemical usage and exposure monitoring information available from the shipyard, the intensity and extent of potential exposures associated with each shop and job was not quantified. In this study, the employment duration was used as a surrogate for cumulative exposure magnitude for each worker who was ever employed in any of the *a priori* jobs or shop categories classified to be associated with exposure was calculated from individual work histories.

Based on the available chemical exposure information, job/shop titles that were of *a priori* interest because of their potential for exposure to benzene and carbon tetrachloride were collapsed into one of six exposure groups. These included the painting, welding, machining, wood working, electrician, and transportation groups. A description of the job collapse for these benzene and carbon tetrachloride exposed groups is included in Appendix H, Table 2.

The welding group consisted of all the welder job titles except welder superintendent and welder supervisory because these two job titles were considered to have only managerial or administrative responsibilities. The welding group also included other related job titles such as flamer cutter, gas cutter/burner, gas plant operator, learner mechanic, acetylene operator, shielding installer, and structural shop general foreman.

The woodworking group consisted of workers with job titles such as joiner, woodworker, and patternmaker. However, job titles commonly associated with carpentry such as carpenters or lofters (construct wooden scale templates) were excluded from this group because these job titles involved mainly construction utilizing wood materials and were not as likely to be exposed to solvents.

The machining group was the largest of the six exposure groups and consisted of job titles that related to occupations involved with both setting up and operating machine tools and the general maintenance, installation, and repair of industrial and marine machinery, tools, and equipment. Job titles in this group included occupations such as machinists, equipment mechanics, machinery workers, maintenance machinists, marine machinists, marine equipment mechanics, marine machinery mechanics, and maintenance mechanics.

The transportation group included workers with job titles that were considered likely to have been exposed to benzene as a contaminant in solvents and petroleum distillates such as gasoline or other fuels. Automotive mechanics, truck drivers, motor vehicle operators, enginemen, crane operators, liquid fuel pump operators, and equipment cleaners are examples of the job titles in this group.

Since individuals at the shipyard were assigned to various organizational shops with various functions, the function of the assigned shop also had to be considered when determining the potential for exposure to benzene and carbon tetrachloride. For example, a painter who was assigned to a production shop would be performing tasks where exposure to these solvents was likely, while a painter assigned to an administrative shop would not be performing tasks with potential exposure. Therefore, shops where the primary function was either production or support of production were considered the shops with benzene and carbon tetrachloride exposure potential. Shops with primarily administrative functions were not considered to have any benzene and carbon tetrachloride exposure potential (Appendix H, Table 1). Individuals who worked in any of the exposed job groups and were assigned to a production or support shop were considered to have experienced potential exposure to benzene and carbon tetrachloride.

This study also incorporated information about the temporal aspects of benzene exposure. Because environmental monitoring for benzene performed in the late 1970s and early 1980s as part of the NIOSH industrial hygiene surveys did not reveal any benzene exposure above current limits, an exposure cut-off date of December 31, 1980 was assigned to all of the exposure job groups except the transportation group. The transportation job group was still considered to have potential benzene exposures until January 1, 1990, when benzene in gasoline was reduced to below 1% in response to requirements enacted by the U.S. Environmental Protection Agency (Kirk et al., 1991). Therefore, a worker employed in the Transportation group would not accumulate exposure time after January 1, 1990, and all other worker's exposure time contribution was considered to have ceased after December 31, 1980.

3.8. Study Variables

3.8.1. Outcome variable

The outcome variable for the study is death from leukemia (all types included) among PNS civilian workers, as defined using the International Classification of Diseases (ICD) revision in effect at the time of death (Table 3.8.1.). The outcome variable is coded as a dichotomous (yes/no) outcome (Table 3.8.3.).

ICD Revision	Years	Leukemia Codes
9th	1979 to 1999	204.0 – 208.9
8th	1968 to 1978	204.0 – 207.9
6th and 7th	1949 to 1967	204.0 – 204.4

3.8.2. Radiation dose metrics

Three radiation dose metrics were calculated. First, cumulative whole body dose for each case and control was calculated by summing measured doses from each monitoring period recorded in shipyard dosimetry records. This cumulative whole body dose was a result of traditional occupational sources of external ionizing radiation as measured by personal radiation dosimeters. Second, the cumulative whole body dose from occupational sources was converted to bone marrow dose using the methods described in section 3.5.8. Third, the cumulative bone marrow dose from all work-related medical x-rays was calculated using methods described in section 3.5.8 and combined with the cumulative bone marrow dose from traditional occupational sources. Radiation doses were truncated for each control when they attained the age at death of their matched case for the three dose metrics.

3.8.3. Description of study covariates

The analysis includes the following covariates, based on the occupational radiation research literature.

- 1) *Gender* is included as a study confounder in the analysis because males have a higher risk of leukemia than females [The American Cancer Society, 2002] and males are expected to have higher doses than females. The analysis of this variable is limited because the PNS cohort is predominately male. Of the 115 leukemia deaths, three (2.6%) are female.
- 2) *Solvent exposure duration* is included in the analysis because of the possibility of increased risk of leukemia among workers exposed to chemical solvents, particularly benzene and carbon tetrachloride, while employed in certain jobs and shops at the shipyard (See Section 3.8). The duration of employment for each worker in any of these job/shop categories was calculated from individual work histories. Solvent exposure was truncated for each control when they attained the age at death for their matched case.
- 3) *Time since last occupational radiation exposure (TSLE)* is included in the analysis because studies have suggested that the level of leukemia risk varies with time since exposure. For example, the Japanese Life Span Study provides evidence that leukemia risk after radiation exposure initially increases for about ten years after exposure, then decreases and largely disappears after 20 years (Darby et al., 1985; Finkelstein, 2000). Also occupational studies examining the temporal patterns of leukemia risk after the end of exposure to benzene report that leukemia risk decreases with the length of time beyond the cessation of exposure, and that this time dependency is similar to those individuals exposed to ionizing radiation (Finkelstein, 2000; Hoel, 1985; Hornung and Meinhardt, 1987; Silver et al., 2002).

TSLE was evaluated first as a continuous variable and then as a categorical variable in the analysis. The categorical analysis includes four categories: category 1 (≥ 5 and <10 years TSLE), category 2 (≥ 2.5 and <5 years TSLE), and category 3 (≥ 0 years and < 2.5 years

TSLE). Each of these three categories is compared to the category of ≥ 10 years of time since last exposure.

For radiation-monitored workers, time since last exposure is the time between the date at which the last exposure occurred and the cutoff date (death from leukemia or date corresponding to matched case's age at death). For non-radiation workers—time since last exposure—is the time between the *date last employed* and the cutoff date. When radiation doses from work-related medical x-rays are included in the analysis, the time since last exposure variable for all workers is defined as the time between either the date of the last medical x-ray examination or last monitoring date (which ever is later) and the cutoff date.

- 4) *The radiation monitoring status of each worker* is included as a dichotomous study variable in the analysis. This variable is included because the PNS cohort study analysis (Silver et al., 2004) reported that leukemia mortality among workers not ever monitored for radiation exposure (SMR = 1.08, 95% CI 0.86, 1.35) differs from radiation-monitored workers who had a recorded exposure (SMR = 0.90, 95% CI 0.60, 1.29) and radiation-monitored workers who had no recorded exposure (SMR = 0.79, 95% CI 0.25, 1.95).

Table 3.8.3. List of Study Variables		
Variable	Type	Comments
Dependent: Leukemia death (underlying cause)	Dichotomous Yes/No	Leukemia death = 1 (case) No leukemia death = 0 (control)
Primary Exposure Variable: Exposure to external ionizing radiation (From occupational & medical x-ray sources)	Continuous	The analysis of the exposure metric will be conducted three ways: 1) Occupational radiation—badge exposure only 2) Occupational radiation—bone marrow dose only 3) Bone marrow dose from both occupational and work-related medical x-rays combined. Quantitative measurements are in mSv.
Possible Effect Modifiers and Confounders		
Variable	Type	Comments
Sex	Categorical	Male = 1, Female = 2
Solvent exposure	Continuous	Never Employed = 0, Employed = 1; in any of the following job/shop categories (Transportation, Welding, Machining, Electrical, Woodworking, Painting and Miscellaneous). Duration of employment was calculated for all workers employed in the seven categories.
Time since last exposure	Continuous & Categorical	Category 1: ≥ 5 and <10 years TSLE Category 2: ≥ 2.5 and <5 years TSLE Category 3: ≥ 0 and 2.5 years TSLE
Radiation Monitoring Status	Categorical	The worker was radiation-monitored (1) or was not radiation-monitored (0).

3.8.4. Covariates not included in the analysis

- 1) *Race* was considered for inclusion in the study analysis because leukemia incidence and mortality is different and generally lower among African-American males than white males (Appendix A, Section 4 and 5). However, race is not included as a study variable for analysis because after reviewing the shipyard medical records for each case and control a determination of race was able to be made for only 444 (77%) of the cases and controls. Because all but four of these 444 cases and controls with known race were white all cases and controls in the study are considered to be white.
- 2) *Smoking* has not generally been considered a major risk factor for leukemia; however, increasing evidence suggests that certain forms of adult leukemia, myeloid and acute nonlymphocytic varieties may be associated with cigarette smoking (Austin and Cole, 1986; Williams and Horm, 1977). Smoking is not included as a study variable in the analysis because of the lack of readily available individual smoking information in the PNS medical records.

3.9. Statistical Analysis

3.9.1. Conditional logistic regression

Conditional logistic regression was used to analyze the study hypothesis and evaluate any exposure-response relationship between external ionizing exposure and leukemia mortality. This type of multivariable analysis is frequently used in matched case-control studies and provides a method to analyze the relationship between a dichotomous outcome and a set of risk variables while controlling for confounding and evaluating effect modification. Conditional logistic regression with incidence density sampling, approximates Cox Proportional Hazards regression (Kleinbaum and Klein, 2002; Szklo and Nieto, 1999).

The initial full conditional logistical regression model is a log-linear model that was parameterized as follows: $\text{Ln} [P(x)/(1-P(x))] = \alpha + \beta_1 (\text{Cum Rad Exp}) + \beta_2 (\text{Radiation Monitoring Status}) + \beta_3 (\text{Sex}) + \beta_4 (\text{Solvent Duration}) + \beta_5 (\text{Time Since Last Radiation Exposure or Date Last Employed})$.

Odds ratios and the corresponding 95% confidence intervals are derived from the parameter estimates and the associated standard errors of the conditional logistic regression model. A two-tailed test of significance with an α level of 0.05 is used to determine statistical significance of the odds ratios and exposure-response relationships.

Because the induction period (period of time from exposure to the development of disease and subsequent death) for leukemia induced by radiation is suspected to be as short as several years (BEIR V, 1990), a separate analysis was conducted in which radiation doses received by cases and controls at zero, two, five, and seven years prior to the date of death of the case are

discounted. As discussed above, all analyses were repeated with the incorporation of medical x-ray dose with occupational dose.

An assessment of possible multiplicative interactions between radiation exposure variables (cumulative badge exposure, cumulative occupational bone marrow dose, and cumulative occupational bone marrow dose combined with work-related medical x-rays) and most of the study covariates (gender, solvent exposure duration, and radiation worker status) was done using a hierarchically formulated approach (Kleinbaum and Klein, 2002). The initial full model (A) included two-way and three-way interactions between the radiation exposure variable and the covariates, and among each of the main effect covariates. It was not possible to evaluate both 2-way or 3-way interactions involving gender and most interactions involving radiation worker status because among the study subjects only males were radiation workers and received a badge exposure. Solvent duration and radiation worker status was the only interaction involving radiation worker status that could be evaluated. The reduced model (B) included all two-way interactions between the radiation exposure variable and the covariates and the main effect covariates; the final reduced model (C) included only the main effects. Statistical testing of interaction terms was performed using a single chunk test for all of the interaction terms in both the full and reduced models (Kleinbaum and Klein, 2002). That is, model C is fully nested within model B, which is fully nested within model A. The statistical test procedure involved first determining the difference between the -2 log likelihood scores and degrees of freedom between the full and reduced models and then between the reduced model and main effects model. The time since last exposure variable was evaluated differently; because it was of *a priori* interest as an effect modifier, its interaction with radiation dose is explored in detail in a sensitivity analysis—Section 4.5.5.

A variable is considered a possible confounder if it is both a leukemia risk factor and associated with radiation dose. The correlations between radiation dose and other covariates are presented in Appendix K, Table 6. Variables that are not considered confounders and cause a greater than 10% change in the parameter estimate of the radiation badge dose metric are kept in the model. Because solvent duration is an occupational exposure of interest it is also retained in the model.

3.10. Analytic Data File Description

3.10.1. Demographic file

The final analytic file for the study includes collected and coded information from three separate files: the demographic file, the work history file, and the radiation exposure file.

The demographic file includes all of the study cases and controls and information such as the worker's name, Social Security Number, date of birth, sex, race (not recorded for all individuals), date of death, ICD-code, and first and last dates employed. This file also assigns a unique identification code for each case and control, which allows for the accurate merger of the three separate files.

3.10.2. Work history file

The United States Navy provided NIOSH with access to the personnel records (United States Government Standard Form 7) of all PNS employees working between January 1, 1952 and December 31, 1996, which were microfilmed and abstracted to the work history database file. This file includes a listing of all the jobs and shops ever assigned to each study subject for the time worked at the shipyard during the study period. Also included are the first and last dates employed in each job and shop assigned.

3.10.3. Radiation exposure file

The occupational radiation exposure records maintained at the shipyard and in individual medical records were collected for each of the radiation-monitored workers. These records contained exposure information from each monitoring period and summaries of monthly, annual, and lifetime exposures. The records also included documentation of prior exposures at locations outside of PNS. The exposure information was abstracted to a dosimetry history file created by NIOSH personnel.

Medical x-ray exposure information was extracted from the medical records for all study subjects and coded into the radiation exposure file. The medical x-ray exposure file includes information such as the x-ray examination date, examination reason (i.e., diagnostic or routine), type of projection (i.e., body part and orientation), and imaging equipment used (i.e., photofluorographic or direct radiographic).

3.11. Data Entry and Quality—Validation

3.11.1. Radiation exposure file

The radiation exposure file was created by blind double coding of the interval exposure information abstracted from the exposure records into a Microsoft Access data base. Cumulative doses were determined (section 3.5.8) from the coded data and compared to the cumulative doses reported by a separate dosimetry file from a previous NIOSH study (Rinsky et al., 1981). Seven individuals had cumulative dose discrepancies of 0.1 mSv or greater, the largest being 2.64 mSv. These discrepancies were investigated further to facilitate the appropriate correction to the final dose file (Daniels et al., 2004a). Based on this analysis, it was determined that the electronic dosimetry file for the study was reasonably correct and was adequate for use in the study analysis.

3.11.2. Work history file

A sample of the hard copy-SF-7 work histories was randomly selected and compared with the electronic work history developed by NIOSH. The sample consisted of the complete work history file for 10% (58 study subjects). There were 1,573 separate entries for the sample, and 6 coding errors were found for an error rate of 0.4 %. It was determined that the work history file for the study is reasonably correct and adequate for use in the study analysis.

4. Results

4.1. Descriptive Statistics

A total of 115 persons were identified in the Portsmouth Naval Shipyard cohort of 37,853 as having died from leukemia. For each case, four controls were selected for a total of 460, five of which were selected twice. The majority of the cases (82%) were born in Maine (40 cases), New Hampshire (34 cases), or Massachusetts (20 cases) (Appendix J, Table 1). Also, the majority of the cases (85%) died in the same three states: New Hampshire (43 cases), Maine (36 cases), and Massachusetts (19 cases) (Appendix J, Table 2).

Among the 115 cases, 34 (30%) were monitored for radiation exposure and 81 (70%) were not monitored. All 34 radiation-monitored cases were male. Of the 81 non-radiation-monitored cases, 78 were males and three were female. Among the 460 controls, 167 (36%) were radiation-monitored (all male) and 293 (63%) were not monitored (253 males and 40 females).

4.1.1. Cause of death information for the cases

The majority (87%) of the 115 leukemia cases were coded in the eighth or ninth revision of the World Health Organization’s International Classification of Diseases (ICD).

Fifteen (13%) of the leukemia cases were coded in the ICD version 6 or 7 (Table 4.1.1.).

Prior to 1968 with publication of the 8th revision to ICD, leukemia subtypes were not separately coded. Of the 115 leukemia cases, 54 (47%) were assigned an ICD code of “unspecified” leukemia, and it was possible to determine from the death certificates that 22 (41%) of the 54 were not chronic lymphocytic leukemia (CLL). Among the remaining 61 specified cases, 28 (46%) were coded as acute monocytic or myeloid leukemia, 14 (23%) were coded as chronic lymphoid leukemia, 11 (18%) were coded as chronic myeloid leukemia, and three (5%) were coded as acute lymphoid leukemia. Three (5%) cases were coded in ICD-6 as “myeloid leukemia” and two (3%) cases were coded in ICD-7 as “lymphoid leukemia.

Table 4.1.1. Frequency of Cases by ICD Code Revisions

ICD Revision	Years	Leukemia Codes	Number of Cases (n=115)
9th	1979 to 1999	204.0 – 208.9	65
8th	1968 to 1978	204.0 – 207.9	35
6th and 7th	1949 to 1967	204.0 – 204.4	15

4.1.2. Temporal variables—cases and controls

The following temporal variables were determined for the cases and controls: the mean year of birth, the mean age at date first employed, mean duration of employment, the mean year first

employed, the mean year last employed, the percent employed for at least five years, the mean time since last employed, and the mean age at the cutoff date (Table 4.1.2). All temporal values were computed as of the cutoff date for each case/control pair.

Temporal Variables	Cases (n = 115)	Controls (n = 460)	p-value
Year of Birth (Mean)	1912	1914	0.24
Age at Date First Employed (Mean)	34.2 yrs.	35.3 yrs.	0.30
Mean Duration of Employment (years)	19.6 yrs.	17.6 yrs.	0.13
Mean Year First Employed	1947	1949	0.06
Mean Year Last Employed	1966	1967	0.46
Percent Employed at least 5 years	79%	76%	0.52
Mean Time Since Last Employed (years)	13.6 yrs.	14.5 yrs.	0.47
Mean Age at Cutoff Date	67.5 yrs.	67.4 yrs.	0.98

There was a year or less difference in the means between the cases and controls for four of the temporal variables. The mean age at date first employed was slightly younger for the cases (34.2 years) than for the controls (35.3 years), and the mean year last employed was one year less for the cases (1966) than for the controls (1967). The mean time since last employed was slightly longer for the controls (14.5 years) than for the cases (13.6 years).

The cases and controls were similar in the percentage of workers employed at least five years (79% for the cases, 76% for the controls) and in mean age at the cutoff date (67.5 years for the cases and 67.4 years for the controls).

In three of the temporal variables, the difference in the means between the cases and controls was greater than a year. The mean year of birth was two years earlier for the cases (1912) than for the controls (1914), the mean year first employed was two years earlier for the cases (1947) than for the controls (1949), and the mean duration of employment was two years longer for the cases (19.6 years) than for the controls (17.6 years). There were no statistically significant differences (Student's *t* test) in the temporal variables between the cases and controls.

4.2 Radiation Exposure Descriptive Statistics

4.2.1. Radiation exposure from occupational sources

Workers who had at least one radiation monitoring period during their employment at the shipyard were classified as radiation-monitored workers. Of the 575 cases and controls, 201 (35%)

were radiation-monitored; 173 (87%) of the radiation-monitored cases and controls had a recorded badge exposure greater than zero and 28 (13%) had zero recorded exposure. Thirty-four (30%) of the 115 leukemia cases and 167 (36%) of the 460 controls were monitored for radiation exposure during their employment at PNS. Five radiation-monitored cases (15%) and 23 radiation-monitored controls (14%) had zero recorded exposure (Table 4.2.1.A.).

The mean and median cumulative occupational badge exposure (results reported by PNS dosimetry without modification except for

Radiation-Monitoring Status	Case (n = 115)	Controls (n = 460)	Total (n = 575)
Radiation-Monitored-Recorded			
Exposure greater than zero	29 (85%)	144 (86%)	173 (86%)
Radiation-Monitored-Recorded Exposure equal to zero	5 (15%)	23 (14%)	28 (14%)
Radiation-Monitored-Total	34 (30%)	167 (36%)	201 (35%)
Non-Radiation Monitored	81 (70%)	293 (64%)	374 (65%)

conversion to SI units) through the cutoff date from onsite (PNS) sources for all radiation-monitored cases and controls combined are 23.17 mSv and 4.52 mSv, respectively. The mean onsite exposure for the cases (38.97 mSv) is almost twice as high as that (19.96 mSv) for the controls. Similarly, the median exposure for the cases (10.44 mSv) is about 2.5 times as great as that (3.82 mSv) for the controls.

The distribution of total cumulative occupational badge exposure is skewed, to the right; the medians of the exposures are smaller than the means due to the number of cases and controls with very low or zero recorded exposures. The collective cumulative occupational badge exposure is 1,325 person mSv for the cases and 3,333 person mSv for the controls. The collective cumulative occupational badge exposure for the cases and controls combined is 4,658 person mSv (Table 4.2.1.B.).

Number of Cases and Controls	Cumulative Onsite Badge Exposure				Collective Badge Exposure (person-mSv)
	Mean (mSv)	Median (mSv)	Min (mSv)	Max (mSv)	
201 (Cases & Controls)	23.17	4.52	0	297.5	4658
34 (Cases)	38.97	10.44	0	190.4	1325
167(Controls)	19.96	3.82	0	297.5	3333

4.2.2. Radiation exposure from offsite sources

Three of the 460 controls had recorded offsite radiation exposure. The mean offsite cumulative badge exposure for these three controls is 3.64 mSv and the median cumulative offsite exposure is 4.83 mSv. There was actual exposure information from previous employers for two of the three controls, accounting for 10.03 mSv or 92% of the offsite exposure. The maximum offsite exposure was 5.20 mSv and the minimum was 0.89 mSv. The offsite exposure accounted for 0.23 % of the total cumulative badge exposure from missed, offsite, and occupational onsite sources combined for the cases and controls.

4.2.3. Estimated missed radiation exposure

Badge exposures were estimated for 175 cases and controls to account for actual exposures that may have been missed due to the variation in measurement sensitivity of the different dosimetry devices. The estimated mean cumulative missed exposure for the 175 cases and controls combined is 0.50 mSv and the median is 0.23 mSv (Daniels et al., 2004b).

The mean estimated missed exposure for the controls (0.49 mSv) is very close to that for the cases (0.54 mSv). The median estimated missed exposure for the cases (0.21 mSv) and controls (0.23 mSv) is also similar. Collective missed exposures totaled 87.6 person mSv, which is 1.84% of the total cumulative badge exposure from missed, offsite, and occupational onsite sources combined for the cases and controls (Table 4.2.3.).

Number of Cases and Controls	Mean (mSv)	Median (mSv)	Min (mSv)	Max (mSv)	Collective Missed Exposure (person-mSv)
175 (Cases & Controls)	0.50	0.23	0.03	3.64	87.6
30 (Cases Only)	0.54	0.21	0.03	3.51	16.2
145 (Controls Only)	0.49	0.23	0.03	3.64	71.4

4.3. Cumulative Bone Marrow Dose Descriptive Statistics

4.3.1. Bone marrow dose estimates from occupational sources

External ionizing radiation exposures from onsite occupational sources were converted from badge exposure values to a cumulative bone marrow dose estimate for each of the 201 radiation-monitored cases and controls. For the radiation-monitored cases and controls, the cumulative bone marrow dose value, which is an estimate of radiation dose to the bone marrow only, is

lower (3,430 person mSv) (Table 4.3.1.) than the cumulative badge exposure value, which is a measure of whole body exposure (4,658 person mSv) (Table 4.2.1.B.). Summary tables of bone marrow dose values for estimated missed and offsite exposures are presented in Appendix K, Tables 1 & 2).

Number of Radiation Monitored Cases and Controls	Mean (mSv)	Median (mSv)	Min (mSv)	Max (mSv)	Collective BMD (person-mSv)
201 (Cases & Controls)	17.06	3.45	0	222.7	3,429
34 (Cases Only)	29.11	7.88	0	144.8	990
167 (Controls Only)	14.60	2.82	0	222.7	2,440

4.3.2. Bone marrow dose estimates from work-related medical x-ray exams

Medical records from the shipyard indicate that external ionizing radiation exposure resulted from work-related medical x-rays that were performed for the following reasons: 1) as part of annual radiation-worker medical qualification examinations; 2) as part of radiation background physical examinations; and 3) as part of mass tuberculosis screenings given (all shipyard employees) in 1948, 1951, 1952, and 1956 (Daniels et al., 2004b).

The cases received a total of 589 work-related medical examinations that included one x-ray compared to 2,110 for the controls. The average number of work-related medical x-ray examinations is similar for the cases and the controls: 5.1 per case and 4.5 per control, respectively (Table 4.3.2.A). However, radiation-monitored cases and controls received an average of 7 work-related medical x-rays compared to 3 for non-radiation-monitored cases and controls (Table 4.3.2.A). This difference is due to primarily to the shipyard practice, discontinued in 1969, of giving a chest x-ray as part of each yearly radiation-worker qualifying physical examination (Daniels et al., 2004b).

Table 4.3.2.A. Frequency by Type of Medical Examination that Included a Work-Related Medical X-Ray for All Cases, All Controls and Radiation-Monitored and Non-Monitored Cases and Controls				
Type of Shipyard Medical Exam that Included an X-ray Exam	All Cases n=115	All Controls n=460	Radiation-Monitored Cases and Controls n=201	Non-Radiation-Monitored Cases and Controls n=374
Radiation Qualification				
Physical	194	572	715	51
Radiation Background				
Physical	28	88	77	39
Mass TB Screening	186	636	285	537
Pre-Employment				
Screening Examination	68	294	123	239
Termination Physical	20	101	41	80
Disability Physical	8	48	26	30
Offsite Physical	11	71	16	66
Other	74	300	203	171
Total*	589	2,110	1,486	1,213
Avg. number of work-related x-rays	5.12	4.5	7.39	3.2

*Includes 164 estimated work-related medical x-rays for 48 cases and controls.

However, mean bone marrow dose values are only moderately higher for the radiation-monitored cases and controls (5.97 mSv) than the non-radiation-monitored cases and controls (4.10 mSv), less than a 2 mSv difference (Table 4.3.2.B.), since monitored workers received greater numbers of x-rays using the lower dose direct radiographic technique. The mean bone marrow dose from work-related medical x-rays for the radiation-monitored cases is 6.63 mSv and is 2.16 mSv greater than the mean for the non-radiation-monitored cases which is 4.47 mSv. There is less difference (1.84 mSv) in the mean bone marrow dose values between the radiation-monitored controls (5.84 mSv) and the non-radiation-monitored controls (4.0 mSv) (Table 4.3.2.B.).

Table 4.3.2.B. Cumulative Bone Marrow Dose from Work-Related Medical X-Rays Given at PNS—Radiation Monitored and Non-Monitored Cases and Controls Separately					
	Mean (mSv)	Median (mSv)	Min (mSv)	Max (mSv)	Collective BMD (person-mSv)
(Rad-Monitored Cases & Controls) n=197	5.97	6.12	0.04	15.08	1,178
(Rad-Monitored Cases Only) n=34	6.63	6.42	0.04	14.08	225.6
(Rad-Monitored Controls Only) n=163	5.84	6.04	0.04	15.08	952.2
Non-Monitored Cases & Controls n=354	4.10	4.50	0.04	16.54	1,454
(Non-Monitored Cases Only) n=77	4.47	4.50	0.04	16.54	344.6
(Non-Monitored Controls Only) n=277	4.00	4.50	0.04	13.50	1,109

However, when the radiation-monitored (n=197) and non-monitored (n=354) cases and controls are combined (Table 4.3.2.C.) the median bone marrow dose values from work-related medical x-rays are the same (4.50 mSv) for the 551 cases and controls combined, the 111 cases and the 440 controls (Table 4.3.2.C.) which illustrates the heavy influence of the workers who had only medical x-ray exposure.

Number of Cases and Controls	Mean (mSv)	Median (mSv)	Min (mSv)	Max (mSv)	Collective BMD (person-mSv)
551 (Cases & Controls)	4.78	4.50	0.04	16.54	2,632
111 (Cases Only)	5.13	4.50	0.04	16.54	570.2
440 (Controls Only)	4.68	4.50	0.04	15.08	2,061

4.3.3. Cumulative bone marrow dose from onsite occupational sources and work-related medical x-rays combined

The collective cumulative bone marrow dose from onsite sources combined with work-related medical x-rays given at PNS was 4,607 person mSv for the 201 radiation-monitored cases and controls. The bone marrow dose from work-related medical x-rays accounted for 26% (1,178 person mSv) of the collective cumulative dose for the radiation-monitored cases and controls. The collective bone marrow dose was 1,216 person mSv for the 34 radiation-monitored cases, 19% (225.6 person mSv) of which was due to work-related medical x-rays. The 167 radiation-monitored controls had a collective dose of 3,392 person mSv, 28% (952.2 person mSv) of which was due to medical x-ray dose (Table 4.3.3.A.).

Number of Cases and Controls	Mean (mSv)	Median (mSv)	Min (mSv)	Max (mSv)	Collective BMD (person-mSv)
201 (Cases & Controls)	22.92	10.70	0.05	236.44	4,607
34 (Cases Only)	35.75	14.51	2.15	147.03	1,216
167 (Controls Only)	20.31	10.33	0.05	236.44	3,392

A bone marrow dose from occupational and work-related medical x-ray doses combined was assigned to 555 radiation-monitored and non-radiation-monitored cases and controls (Table 4.3.3.B.). Only 4 cases and 16 controls had no bone marrow dose from any source being considered in this study. The collective cumulative bone marrow dose from occupational sources and work-related medical x-rays combined for the 555 cases and controls was 6,061 person mSv of which 43% (2,632 person mSv) was from work-related medical x-rays. The 111 cases had a collective dose of 1,560 person mSv, of which 37% (570.2 person mSv) was from work-related medical x-rays.

The 444 controls had a collective dose of 4,501 person mSv, of which 46% (2,061 person mSv) was from work-related medical x-rays (Table 4.3.3.B.). The percentage of the collective cumulative bone marrow dose from work-related medical x-ray exposure is greater among the 555 cases and controls than the 201 radiation-monitored workers (43% vs. 26%) because 354 of the 555 cases and controls had bone marrow dose from medical x-rays only and no bone marrow dose from occupational exposures.

Number of Cases and Controls	Mean (mSv)	Median (mSv)	Min (mSv)	Max (mSv)	Collective BMD (person-mSv)
555 (Cases & Controls)	10.92	4.62	0.04	236.4	6,061
111 (Cases Only)	14.05	6.0	0.04	147.0	1,560
444 (Controls Only)	10.13	4.54	0.04	236.4	4,501

4.4. Solvent Exposure Duration Descriptive Statistics

There were 63 cases and 244 controls identified as employed in job and shop categories likely to involve benzene and carbon tetrachloride exposure (Table 4.4). The mean and median values for cumulative employment duration in any of the exposed groups were 14.5 and 14.3 years for the cases and 10.0 and 7.7 years for the controls. The machining group included more cases (30) and controls (112) than any of the other exposed groups. The mean and median cumulative employment duration in the machining group was 15.6 and 16.1 years for the cases and 10.7 and 10.1 years for the controls (Table 4.4). Distributions of solvent duration (years) for radiation-monitored and non-monitored cases and controls appears in Appendix K, Tables 33-36.

PNS Job/Shop	Cases	Controls	Mean Duration (yrs.) (Cases)	Median Duration (yrs.) (Cases)	Mean Duration (yrs.) (Controls)	Median Duration (yrs.) (Controls)
Painting Group	2	12	13.0	13.0	9.2	8.8
Welding Group	11	34	14.0	13.1	11.4	7.8
Transportation Group	9	27	9.3	5.8	5.2	3.0
Electrical Group	19	44	8.0	6.1	9.9	5.5
Machining Group	31	113	15.6	16.1	10.7	10.1
Woodworking Group	3	28	4.1	2.5	5.9	2.1
Total Solvent Exposed Group*	63	244	14.5	14.3	10.0	7.7

*There were 26 cases and controls that were included in more than one Job/Shop Group

4.5. Results of Conditional Logistic Regression Analysis

The conditional logistic regression analysis, which assumes a log-linear model, includes the evaluation of the exposure-response relationship between external ionizing radiation and leukemia mortality among PNS civilian workers. The whole-body radiation exposure variable includes estimated missed exposures and exposures received from onsite and offsite sources. The analysis involved in the selection of the lag period, assessment of interactions, and evaluation of confounding is described and the results of the final model reported. Separate analysis excluding estimated missed radiation exposure and exposure from offsite sources from the radiation exposure variable is included. Also, the impact of exposure from work-related medical x-rays on leukemia risk is reported. A description of the source of radiation exposure included in the radiation dose variable in each table in section 4.5 – 5.0 is located in Appendix K, Table 30.

4.5.1. Determination of lag period —primary exposure variable—cumulative radiation badge exposure

Lag periods of zero, two, five, and seven years were evaluated using the likelihood ratio statistic test with whole body radiation exposure (onsite, offsite, and estimated missed exposures combined) as the only variable included in the model. The estimated missed exposure portion of the variable was not lagged because it was not assigned to specific time periods. While there was little difference in the odds ratios and confidence limits among the lag periods, the two-year lag was chosen for use in remaining modeling because of the slightly higher likelihood ratio test, biological plausibility, and previous research literature (BEIR V, 1990). The odds ratio, 95% CI, likelihood ratio test chi-square, and *p*-value for each lag period are listed in Table 4.5.1.

Exposure Variable (1 mSv)	Parameter DF	Estimate	SE	Odds Ratio	95% Confidence Limits	LR Test Chi-Sq	Pr > Chi-Sq
Occupational Badge Exposure Zero Lag	1	0.00410	0.00304	1.00	0.99 1.01	1.68	0.20
Occupational Badge Exposure Lagged 2 Years	1	0.00422	0.00306	1.00	0.99 1.01	1.76	0.18
Occupational Badge Exposure Lagged 5 Years	1	0.00424	0.00317	1.00	0.99 1.01	1.65	0.20
Occupational Badge Exposure Lagged 7 Years	1	0.00421	0.00324	1.00	0.99 1.01	1.55	0.21

*Includes onsite badge plus offsite and missed exposure.

4.5.2. Assessment of interactions with the primary exposure metric—cumulative radiation badge exposure

An assessment of possible interactions between radiation badge exposure, as the primary exposure variable, and the study variables (gender, solvent exposure duration, time since last (radiation) exposed and radiation worker status) was conducted. Interaction between radiation badge exposure and solvent duration and radiation worker status and solvent duration was evaluated. It was not possible to evaluate any 2-way or 3-way interactions involving gender and most interactions involving radiation worker status because only males were radiation workers and had a badge exposure data. Time since last exposure was included as a main effect in each

model, and was included as an interaction term with cumulative radiation exposure in a separate test—described in section 4.5.5—as it was expected *a priori* that this is an important interaction to analyze based on the literature (BEIR V, 1990).

When the full model (A) is compared to the reduced model (B), there is no significant difference; therefore, the interactions in the full model were dropped. When the reduced model (B) is compared to the main-effects-only model (C), there is no significant difference and the 2-way exposure interactions were dropped, leaving the main-effects-only model (Table 4.5.2.A). All of the variables included in both models A and B are included in Appendix K, Tables 3 & 4.

Model	-2 LOG L DF	-2 LOG L With Covariates	-2 LOG L With Covariates Differences	Critical Value- Chi-Sq (0.05)
A) Full model with 2-way interactions and main effects Interactions Included (Occupational badge exposure-2 yr lag * solvent duration) and (radiation worker status * solvent duration) (Appendix K Table 3)	9	341.79		
B) Reduced model 2-way exposure interactions and main effects Interaction Included (Occupational badge exposure * solvent duration interaction) (Appendix K Table 4)	8	342.01	B-A = 0.22 1 df	3.84
C) Reduced model—main effects (Table 4.5.2.B)	7	343.24	C-B = 1.24 1 df	3.84

Variables in the main effects model (C), gender, radiation worker status, solvent exposure duration, and time since last exposure were evaluated as possible confounders. A variable was considered a possible confounder if there is a greater than 10% change in the parameter estimate of the radiation badge exposure variable when the variable is removed from the model.

Variables that are determined not to be confounders are considered for removal from the model. Gender is considered a confounder—and left in the model—because its removal causes a 12% change in the radiation exposure parameter estimate (Appendix K, Table 5).

The solvent exposure duration variable is not a confounder; when removed from the model, the change in the radiation badge exposure parameter estimate is only 7% and it is not correlated

with badge exposure ($p=0.14$) (Appendix K, Tables 5 & 6). While consideration was given to removing the variable from the model it was kept because it is an occupational exposure of interest. Radiation worker status is considered a confounder—and left in the model—because its removal causes an 80% change in the radiation badge exposure parameter estimate (Appendix K, Table 5).

Table 4.5.2.B. Main Effects Model—2 Year Lag

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Confidence Limits	
							(10mSv)	(1 mSv)
Occupational Badge Exposure Lagged 2 Years	1	0.0082	0.0036	5.291	0.021	1.09	1.01	1.16
Gender (1=Female, 0=Male)	1	-1.235	0.6141	4.045	0.044	0.29	0.09	0.97
Radiation Worker flag (1=Yes, 0=No)	1	-0.8255	0.2726	9.173	0.0035	0.44	0.26	0.75
Solvent Duration Exp - Lagged 2 Years	1	0.0348	0.0117	8.889	0.0039	1.04	1.01	1.06
TSLE is ≥ 5 year and <10 years	1	-0.1718	0.3604	0.2274	0.6345	0.84	0.42	1.71
TSLE is ≥ 2.5 years and <5 years	1	0.6625	0.4072	2.647	0.1048	1.94	0.87	4.31
TSLE is ≥ 0 years and <2.5 years	1	-0.4926	0.4112	1.435	0.2319	0.61	0.27	1.37

TSLE was first evaluated as a continuous variable and was not significant in the main effects model (OR=0.99; 95% CI=0.98, 1.02) (Appendix K, Table 28). No interactions involving TSLE as a continuous variable were found to be significant (Appendix K, Tables 25–27).

The time since last exposure (TSLE) variable was also modeled as a categorical variable and included the following three categories: category 1 (≥ 5 years TSLE and <10 years TSLE), category 2 (≥ 2.5 years and <5 years TSLE), and category 3 (0 years TSLE and <2.5 years TSLE). Each of the three categories was compared to the fourth category of ≥ 10 years of time since last exposure.

The categorical variable time since last exposure is not a confounder because when removed from the model there is only a 7% change in the radiation badge exposure variable and there is no significant correlation between any of the categories and the radiation exposure and case status variables (Appendix K, Tables 5 & 6). There was not a significant elevation of leukemia mortality in any of the TSLE categories but there was a non-significant elevation of the odds ratio in the ≥ 2.5 years and < 5 years TSLE category (OR=1.94; 95% CI=0.87, 4.31) (Table 4.5.2.B). The variable was dropped from the model, but its role as an effect modifier is explored in section 4.5.5.

4.5.3. Final regression model—occupational badge exposure

The final log-linear model includes a significant positive exposure response relation between disease (leukemia mortality) and exposure (external ionizing radiation), adjusting for gender, radiation worker status, and solvent exposure duration (OR=1.08 at 10 mSv of exposure; 95% CI=1.01, 1.16). The final model was also analyzed using a linear excess relative risk model which yielded higher risk estimates (RR = 1.02 at 1 mSv; 95% likelihood-based CI=1.00, 1.09; and RR = 1.23 at 10 mSv; 95% likelihood-based CI= 1.03, 1.88) than the log linear model. A table of the risk coefficients by dose category using the log-linear model appears in Appendix K Table 37.

To evaluate the potential impact of estimated missed radiation exposure and radiation exposure from offsite sources, the radiation exposure variable in the final log-linear model was modified by excluding exposure from both of these sources. When the radiation exposure variable includes only badge exposure from onsite occupational sources, there is still a significant positive exposure response between leukemia mortality and radiation exposure and the odds ratio and confidence limits remain essentially unchanged (OR=1.08 at 10 mSv of exposure; 95% CI=1.01, 1.16) (Appendix K, Table 7).

The log-linear model results also include a significant positive exposure response between leukemia mortality and the duration of time worked in any of the *a priori* solvent-exposed job and shop categories—painting, welding, transportation, electrical, machining, and woodworking—(OR= 1.03 at one year of exposure; 95% CI=1.01, 1.06).

The parameter estimate for radiation worker status in the log-linear model is negative (Table 4.5.3.) and reflects the fact that radiation-monitored workers had a lower overall leukemia risk than non-monitored workers, which is a finding that is supported by a previous NIOSH mortality study (Silver et al., 2004).

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Confidence Limits	
Badge Exposure Lagged 2 Years	-					(10 mSv) 1.08	1.01	1.16
						(1 mSv) 1.01	1.00	1.02
Gender	1	-1.194	0.6112	3.816	0.0508	0.30	0.09	1.00
Radiation Worker flag (1=Yes, 0=No)	1	-0.7283	0.2632	7.660	0.0056	0.48	0.29	0.81
Solvent Duration Exp - Lagged 2 Years	1	0.0323	0.0115	7.855	0.0051	1.03	1.01	1.06

4.5.4. Final regression model using bone marrow dose

External ionizing radiation exposures (estimated missed exposures and exposures from onsite and offsite sources combined) were converted to a cumulative bone marrow dose estimate for each case and control so that impact of exposures from work-related medical x-rays could be analyzed. A lag period of two years was selected using the likelihood ratio test for the analysis of the occupational bone marrow dose separately and combined with work-related medical x-ray dose (Appendix K, Tables 8 & 9). The model fit statistics show that there were no significant interaction terms found in the model that includes only occupational bone marrow dose (full vs. reduced: $-2 \log L = 0.21$ 1df; $p = 0.64$; reduced vs. main effects: $-2 \log L = 1.23$ 1 df; $p = 0.26$) (Appendix K Table 10) or the model that combines bone marrow dose from both occupational sources and work-related medical x-rays (full vs. reduced: $-2 \log L = 2.56$ 2df; $p = 0.28$; reduced vs. main effects: $-2 \log L = 1.25$ 3 df; $p = 0.74$) (Appendix K, Table 14). All of the interaction terms for both the full and reduced models for both the occupational bone marrow dose only model and the model combining occupational and medical x-ray bone marrow dose are listed in (Appendix K, Tables 11,12, 13 & 15, 16, 17).

4.5.4.1. Final log-linear regression model—primary exposure variable—bone marrow dose from occupational sources

In the final regression model with only bone marrow dose from occupational radiation exposure included, there is a significant positive dose response between leukemia mortality and bone marrow dose adjusting for gender, radiation worker status, solvent exposure duration, and time since last exposed. The odds ratio is 1.11 at 10 mSv of exposure and the 95% CI = 1.01, 1.22 (Table 4.5.4.1). The increase in the leukemia risk estimate with occupational bone marrow dose

only compared to the model with occupational badge exposure only (OR=1.08 at 10 mSv of exposure; 95% CI=1.01, 1.16) because there is less (1,258 mSv) cumulative bone marrow dose than whole body exposure (Appendix K, Table 19).

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Confidence Limits	
							(10 mSv)	(1 mSv)
Occ BMD Lag 2 Years	1	0.0105	0.0047	5.031	0.0249	1.11	1.01	1.22
Gender	1	-1.193	0.6111	3.813	0.0509	0.30	0.092	1.00
Radiation Worker (1=Yes, 0=No)	1	-0.7312	0.2629	7.737	0.0054	0.48	0.29	0.81
Solv Duration Exp - Lag 2 Years	1	0.0323	0.0115	7.865	0.0050	1.03	1.01	1.06

4.5.4.2. Final regression model—primary exposure variable—occupational bone marrow dose combined with medical x-ray bone marrow dose

When bone marrow dose from exposure due to work-related medical x-rays is combined with dose from occupational sources (including estimates from missed doses and offsite sources) the dose response is significant (OR=1.11 at 10 mSv of exposure; 95% CI= 1.02, 1.22) (Table 4.5.4.2) and almost identical to that of the model that includes only occupational bone marrow dose (OR=1.11 at 10 mSv of exposure; 95% CI= 1.01, 1.22) (Table 4.5.4.1).

An analysis combining bone marrow dose from only onsite occupational sources (excluding estimates from missed doses and offsite sources) with work-related medical x-rays was conducted. The exposure response relationship between leukemia mortality and bone marrow dose remains almost unchanged with the exclusion of missed and offsite dose (OR = 1.16 at 10 mSv of exposure; 95% CI= 1.09, 1.22) (Appendix K, Table 18).

Both models with and without work-related medical x-ray dose included show a significant positive exposure response between disease (leukemia mortality) and the duration of time workers were exposed to solvents, adjusting for gender and radiation worker status (Tables 4.5.4.1 & 2).

Variable	DF	Parameter Estimate	Standard Error	Chi-Sq	Pr > ChiSq	Odds Ratio	95% Confidence Limits	
Occupational Cumulative BMD + Work-Related Medical X-Ray Dose - Lagged 2 Years	1	0.0108	0.0046	5.571	0.0183	(10 mSv) 1.11	1.02	1.22
Gender	1	-1.198	0.6110	3.843	0.0500	(1 mSv) 1.01	1.00	1.02
Radiation Worker (1=Yes, 0=No)	1	-0.7581	0.2660	8.123	0.0044	0.30	0.09	1.00
Solvent Duration Exposed – Lagged 2 Years	1	0.0312	0.0115	7.366	0.0066	1.03	1.01	1.06

4.5.5. Sensitivity analysis—badge exposure and time since last exposure variable interaction

An evaluation of the interaction between each of the time since last exposure (TSLE) categories and the radiation exposure variable were evaluated. There were two analyses, each using different TSLE categories. The variance covariance tables generated from SAS and the formula that was used to derive the parameter estimates, standard error, odds ratio, and 95% confidence interval for each interaction are located in Appendix K, Tables 20–22.

The first analysis modeled the time since last exposure (TSLE) variable using the following four categories: category 1 (> 10 years TSLE), category 2 (≥ 5 years TSLE and <10 years TSLE); category 3 (≥ 2.5 years and <5 years TSLE); and category 4 (≥ 0 years TSLE and <2.5 years TSLE). The coefficients for these interactions were used to calculate the exposure-response trends for each of the four different TSLE categories. The exposure variable included in each interaction was modeled at both 1 and 10 mSv (Tables 4.5.5.A. & 4.5.5.B.).

The odds ratios for the interactions between radiation exposure and the ≥ 10 years TSLE category, the ≥ 5 years and <10 years TSLE category, the ≥ 2.5 years and <5 years TSLE category, show evidence of substantial interaction (Likelihood Ratio Test (LRT) = 8.28. $p=0.04$). The wave-like odds ratio pattern indicate that the exposure-response relationships are possibly different among the TSLE categories with the exposure response relationship elevated but not significant in the ≥ 0 and < 2.5 years TSLE, and significantly elevated in the ≥ 2.5 year and < 5 year TSLE category and decreasing in the ≥ 5 year and < 10 year TSLE category (Table 4.5.5.A). However, the ≥ 2.5 year and < 5 year TSLE group which is the only one exhibiting a significant exposure response relationship has fewer cases and controls ($n=42$) than the other groups.

Variable	DF	Parameter Estimate	Standard Error	Odds Ratio (1 mSv)	95% Confidence Limits	
Cum Rad Exposure at ≥ 10 year TSLE	1	0.0071	0.0040	1.01	0.99	1.02
Cum Rad Exposure at ≥ 5 and <10 years TSLE	1	-0.0408	0.0417	0.96	0.89	1.04
Cum Rad Exposure at ≥ 2.5 and <5 years TSLE	1	0.0507	0.0214	1.05	1.01	1.10
Cum Rad Exposure at ≥ 0 and <2.5 years TSLE	1	0.0090	0.0081	1.01	0.99	1.03

*Risk estimates for main effects are similar to those in the analysis without radiation exposure and TSLE interactions and are not listed.

As a test of the sensitivity of the TSLE/radiation exposure interaction to the categorization scheme employed, the second analysis modeled the TSLE variable using the following three categories: category 1 (> 7 years TSLE), category 2 (> 3 years and

≤ 7 years TSLE), and category 3 (≥ 0 years TSLE and ≤ 3 years TSLE). The coefficients for these interactions represent the exposure-response relationships among the three different TSLE categories. The exposure variable included in each interaction was modeled at both 1 and 10 mSv (Tables 4.5.5.C. & 4.5.5.D.).

Variable	DF	Parameter Estimate	Standard Error	Odds Ratio (10 mSv)	95% Confidence Limits	
Cum Rad Exposure at ≥ 10 year TSLE	1	0.0709	0.0396	1.073	0.99	1.16
Cum Rad Exposure at ≥ 5 and <10 years TSLE	1	-0.3857	0.417	0.68	0.30	1.54
Cum Rad Exposure at ≥ 2.5 and <5 years TSLE	1	0.5068	0.2147	1.66	1.09	2.52
Cum Rad Exposure at ≥ 0 and <2.5 years TSLE	1	0.0953	0.0768	1.10	0.94	1.28

*Risk estimates for main effects are similar to those in the analysis without radiation exposure and TSLE interactions and are not listed.

The odds ratios for the interactions between radiation exposure and the > 7 years TSLE category, the >3 years and ≤ 7 years TSLE category, and the ≥ 0 years and ≤ 3 years TSLE category also show evidence for significant interaction (LRT = 7.27, $p=0.03$). As in the first analysis the odds ratios indicate that the exposure-response relationships are possibly different among the TSLE categories (Table 4.5.5.C). The exposure response relationship is elevated but not significantly in the ≥ 0 and ≤ 3 year TSLE category, significantly elevated in the >3 years and ≤ 7 year TSLE category and again decreases in the > 7 year TSLE category. While lengthening the ≥ 2.5 and < 5 year TSLE category in the first analysis to > 3 and ≤ 7 years TSLE in the second analysis did increase the number of cases and controls—from 42 to 56—however, the number of cases (12) remained unchanged.

Table 4.5.5.C. Cumulative Badge Exposure Variable—No Lag—and Three TSLE Category Variable Interactions*

Variable	DF	Parameter Estimate	Standard Error	Odds Ratio (1 mSv)	95% Confidence Limits	
Cum Rad Exposure at > 7 year TSLE	1	0.0062	0.0039	1.006	0.99	1.01
Cum Rad Exposure at >3 and ≤ 7 years TSLE	1	0.0488	0.0174	1.050	1.02	1.09
Cum Rad Exposure at ≥ 0 and ≤ 3 years TSLE	1	0.0070	0.0078	1.007	0.99	1.02

*Risk estimates for main effects are similar to those in the analysis without radiation exposure and TSLE interactions and are not listed.

Table 4.5.5.D. Cumulative Badge Exposure Variable—No Lag—and Three TSLE Category Variable Interactions*

Variable	DF	Parameter Estimate	Standard Error	Odds Ratio (10 mSv)	95% Confidence Limits	
Cum Rad Exposure at > 7 year TSLE	1	0.0699	0.0393	1.064	0.99	1.15
Cum Rad Exposure at > 3 and ≤ 7 years TSLE	1	0.4916	0.1737	1.635	1.16	2.30
Cum Rad Exposure at ≥ 0 and ≤ 3 years TSLE	1	0.0685	0.0782	1.071	0.92	1.25

*Risk estimates for main effects are similar to those in the analysis without radiation exposure and TSLE interactions and are not listed.

4.5.6. Sensitivity analysis—occupational and work-related medical x-ray bone marrow dose combined and time since last exposure variable interaction

Possible interactions between each of the TSLE categories and the bone marrow dose from occupational sources and work-related medical x-rays combined were also evaluated. For this analysis the time since last exposure variable is defined as the time between either the date of the last medical x-ray examination or last monitoring date (which ever is later) and the cutoff date. The variance covariance tables generated from SAS and the formula that was used to derive the parameter estimates, standard error,

odds ratio, and 95% confidence interval for each interaction are located in Appendix K, Tables 20, 23 and 24.

This analysis modeled the TSLE variable using the following categories: category 1 (>10 years TSLE), category 2 (≥ 5 years TSLE and <10 years TSLE), category 3 (≥ 2.5 years and <5 years TSLE), and category 4 (≥ 0 years TSLE and <2.5 years TSLE). The coefficients for these interactions represent the exposure-response relationships for each of the four TSLE categories. The exposure variable included in each interaction was modeled at 1 mSv (Table 4.5.6.A.). The odds ratios for the interactions between bone marrow dose and the different TSLE categories are also listed in Table 4.5.6.A.

Variable	DF	Parameter Estimate	Standard Error	Odds Ratio (1 mSv)	95% Confidence Limits	
Occ + X-Ray Dose at ≥ 10 year TSLE	1	0.0091	0.0059	1.01	0.99	1.02
Occ + X-Ray Dose at ≥ 5 and <10 years TSLE	1	0.0188	0.0134	1.02	0.99	1.05
Occ + X-Ray Dose at ≥ 2.5 and <5 years TSLE	1	0.0100	0.0115	1.01	0.99	1.03
Occ + X-Ray Dose at ≥ 0 and <2.5 years TSLE	1	0.0109	0.0094	1.01	0.99	1.03

*Risk estimates for main effects are similar to those in the analysis without radiation exposure and TSLE interactions and are not listed.

The odds ratios are very similar and range from 1.01 to 1.02 respectively (Table 4.5.6.A.). Unlike the analysis of interactions between TSLE categories and occupational badge exposure model, there is no evidence for substantial interaction between the TSLE categories and occupational plus work-related medical x-ray exposures (LRT = 0.49, $p=0.92$ and Tables 4.5.6.A.).

The second analysis modeled the time since last exposure (TSLE) variable using the following three categories: category 1 (> 7 years), category 2 (>3 years and ≤ 7 years TSLE); and category 3 (≥ 0 years TSLE and ≤ 3 years TSLE). The coefficients for these interactions represent the exposure-response relationships among the three different TSLE categories. The exposure variable included in each interaction was modeled at 1 mSv (Tables 4.5.6.B).

The odds ratios for the interactions between radiation exposure and the different TSLE categories are listed in Table 4.5.6.B. The interaction is not significant (LRT=0.0843, $p=0.96$). As indicated, the odds ratios are very similar (ORs = 1.01). The possibility of an exposure response relationship is borderline in the > 7 years TSLE category, however the result is not significant (OR=1.01 (95%CI=1.00, 1.02).

Variable	DF	Parameter Estimate	Standard Error	Odds Ratio (1 mSv)	95% Confidence Limits	
Occ + X-Ray Dose at > 7 year TSLE	1	0.0111	0.0055	1.01	1.00	1.02
Occ + X-Ray Dose at >3 and ≤ 7 years TSLE	1	0.0139	0.0116	1.01	0.99	1.04
Occ + X-Ray Dose at ≥ 0 and ≤ 3 years TSLE	1	0.0100	0.0092	1.01	0.99	1.03

*Risk estimates for main effects are similar to those in the analysis without radiation exposure and TSLE interactions and are not listed.

5. Discussion

This case-control study of 115 leukemia deaths at the Portsmouth Naval Shipyard evaluated the relation between external ionizing radiation dose and leukemia mortality after potential confounders and effect modifiers such as solvent exposure, radiation worker status, and age were considered. Lag assumptions of 0, 2, 5, and 7 years were tested first with each radiation dose term individually and then in each final regression models. The two-year lag was determined by both methods to be the best fit and was used in all regression models in the study analysis. Radiation doses lagged 2 years for both the radiation-monitored cases and controls appears in Appendix K, Tables 31-32.

A positive association was found with a log-linear model between leukemia mortality and increasing external ionizing whole-body radiation exposure, after adjusting for radiation worker status and solvent exposure duration (OR=1.01 at 1 mSv; 95% CI=1.00, 1.02 and OR=1.08 at 10 mSv; 95% CI=1.01, 1.16). When the radiation exposure variable was modified (by removing pre-PNS occupational radiation exposure contained in an individual’s record and estimated missed radiation exposure) to include only exposure that occurred onsite, the odds ratio and confidence limits remained unchanged (Appendix K, Table 7). Both offsite and missed radiation

exposures combined accounted for only 2% of the total badge exposure for the cases and controls. The interaction between age and radiation badge exposure was assessed and found to be not significant ($p = 0.07$). Also, a birth cohort analysis was conducted and revealed no differences in leukemia mortality among birth cohort groups. A linear excess relative risk model was also used and yielded higher risk estimates (RR 1.02 at 1 mSv; 95% likelihood-based CI=1.00, 1.09, and 1.23 at 10 mSv; 95% likelihood-based CI= 1.03, 1.88) than the log linear model.

Analyses were conducted using both the log linear and linear ERR models, excluding all cases and controls with more than 100 mSv of cumulative external ionizing radiation dose to illustrate the effect on the risk estimates and confidence intervals without highly exposed subjects. The log linear model exhibited no change in the point estimate; however, the confidence interval does include one (OR=1.01 at 1 mSv; 95% CI= 0.99, 1.03). The linear ERR model also exhibited no change in the point estimate, and the confidence interval also includes one (RR= 1.02 at 1 mSv; 95%CI=0.99, 1.11)

Because some analyses of leukemia risk in nuclear workers have shown an increase in the risk estimate when chronic lymphocytic leukemia (CLL) cases are excluded, an analysis in this study was also conducted excluding CLL cases. The significant exposure response remained unchanged when all 14 of the cases identified with CLL were excluded from the analysis. Of the 14 cases of CLL, three had a history of radiation exposure. Added together, their collective exposure was only 50.33 person mSv.

The finding of a significant exposure-response relationship between leukemia mortality and radiation exposure is consistent with the most recent NIOSH studies of PNS workers. Analysis of the source cohort (Silver et al. 2004), exhibited no overall increase in leukemia mortality (SMR = 1.01, 95% CI = 0.84, 1.22), but the Standardized Risk Ratio (SRR) was significantly increased in some groups of workers. Silver et al. (2004) reported significant elevations in leukemia mortality with increased exposure among radiation-monitored workers who received between 10 mSv and 49.9 mSv and those with more than 50 mSv of total cumulative radiation exposure compared to workers who received less than 1 mSv of cumulative radiation exposure. The trend test over the four exposed groups was statistically significant. However, their study did not incorporate medical x-ray dose, nor did it consider confounding or effect modification.

The positive dose-response pattern for leukemia reported by Silver et al. was also observed in a recent analysis of 13,468 PNS radiation-monitored workers by Yiin et al. (2004). A non-statistically significant elevation in excess relative risk (ERR) of 10.9% (95% CI = - 0.09%, 38.0%) per 10 mSv of external radiation exposure, was observed after potential confounders were considered in the analysis (Yiin et al., 2004).

In this study, the linear ERR model estimated an excess relative risk of 23% (95% CI = 3%, 88%) per 10 mSv of external radiation exposure from occupational sources after potential

confounders were included. The ERR has been estimated in previous studies between -4.1% and 19.0% at 10 mSv for workers exposed to penetrating ionizing radiation (Fraser et al., 1993) and approximately 4% for individuals in the Japanese Life Span Study who were simultaneously exposed at various ages and developed diseases at different times after exposure (BEIR V, 1990; Schubauer-Berigan and Wenzl, 2001). In contrast, workers receive fractionated exposures over periods of time, often several decades in length. A linear quadratic model is often used in analyses of individuals in the Japanese Life Span Study because it fits data better than a simple linear model (BEIR V, 1990; Ron, 1998). The addition of a quadratic term, however, did not improve the model fit in the linear ERR analyses used in this case-control study.

A statistically significant positive relationship was found between leukemia mortality and the duration of time workers were employed in six *a priori* determined job categories (machining, transportation, welding, electrical, painting, and woodworking) determined to have had potential exposure to benzene or carbon tetrachloride. The association between radiation exposure and leukemia was not confounded by employment in these job categories where solvent exposure may have occurred. When work in the categories is removed from the regression model there is a less than 10% change in the radiation exposure parameter estimate. Because the variable is not significantly correlated with radiation exposure ($p = 0.14$) and not a confounder, it appears that it may present an excess leukemia mortality risk that is independent of the excess risk from radiation exposure. Yiin et al. (2004) reported an elevated but not significant leukemia risk among 13,468 radiation-monitored-workers ever exposed to solvents (RR=1.14; 95% CI = 0.56, 2.34). It is important to note that the solvent exposure metric in the cohort-level analysis of the radiation-monitored workers was dichotomous (ever/never worked in a potentially exposed job), unlike in our case-control study, where it was feasible to utilize detailed work history information to determine the amount of time each worker was actually employed in jobs with potential solvent exposure. When the dichotomous solvent exposure metric was used in this case-control study, it also was not significant.

Time Since Last (radiation) Exposure (TSLE) was first evaluated as a continuous variable and found not to be statistically significant (OR=0.99 at one year; 95% CI=0.98, 1.02) (Appendix K, Table 28). There was also no statistically significant interaction between TSLE (as a continuous variable) and radiation exposure, (OR= 1.00; 95% CI = 0.99, 1.00) (Appendix K, Table 27). The TSLE variable was then modeled as a categorical variable using the following categories: category 1 (≥ 5 years TSLE and <10 years TSLE), category 2 (≥ 2.5 years and <5 years TSLE), and category 3 (0 years TSLE and <2.5 years TSLE). Each of the three categories was compared to the fourth category of ≥ 10 years of time since last exposure. As with the continuous variable analysis, there was no significant elevation of leukemia mortality in any of the TSLE categories, but there was a non-significant elevation of the odds ratio in the ≥ 2.5 years and <5 years TSLE category (OR=1.94; 95% CI=0.87, 4.31) (Table 4.5.2.B).

Finally, in a separate analysis we examined the interaction between radiation exposure and the different TSLE categories. A significant exposure-response relationship was found in the 2.5 – 5

years since last exposure category compared to the > 10 years since last exposure category indicating that there is evidence of heterogeneity in the radiation exposure-response relationships among different time since last exposed categories. The choice of categories for TSLE categorical classification did not greatly alter these findings as there was also a significant exposure-response relationship found in the 3–7 years since last exposure category compared to the > 7 years since last exposure category.

This finding helps describe the temporal dynamics of leukemia risk following radiation exposure and is supported by other study findings. Studies of individuals in the Japanese Life Span Study and medically exposed cohorts have reported a wave-like pattern of leukemia risk after exposure, with peaks observed from approximately 5 to 15 years after exposure which then decrease (Little et al., 1999; BEIR V, 1990; Schubauer-Berigan and Wenzl, 2001). Studies of 21,500 Russian nuclear workers at the Mayak complex who received very high radiation exposures also report the pattern (Shilnikova et al., 2003).

An evaluation of leukemia mortality and radiation exposure was also done using a time windows of exposure approach described by Rothman (Rothman & Greenland, 1998). The total radiation exposure accrued by each case and control in the period $0 < 2.5$ years prior to case failure (or, for controls, prior to the attained age of the case), $2.5 < 5$ years prior, $5 < 10$ years prior and ≥ 10 years prior was determined. Then the association between leukemia mortality and total exposure accrued in each window of exposure was examined.

As with the approach using total lifetime cumulative radiation exposures in the interaction with TSLE categories, the leukemia risk using the windows of exposure approach appears to be heterogeneous. While the effect estimate is elevated in the $2.5 < 5$ year exposure window (OR=1.02 at 1 mSv; 95% CI= 0.94, 1.11), the total radiation dose between $5 < 10$ years appears to have the greatest effect on leukemia mortality (OR=1.04 at 1 mSv; 95% CI= 1.00, 1.07) and the effect estimate declines in the window ≥ 10 years (OR=1.01 at 1 mSv; 95% CI= 0.99, 1.01) (Appendix K Table 29). The window of exposure method better accounts for the fact that radiation exposures at PNS were not single, acute exposures (in which time since exposure is easily defined) but are protracted exposures with different times since exposure for each recorded exposure.

It was observed in this study that the incorporation of dose from work-related medical x-ray exposures does not change the leukemia risk estimate. When the regression model includes bone marrow dose from both occupational sources and work-related medical x-rays, there is a significant dose response. However, when the bone marrow dose from work-related medical x-rays is removed, the dose-response relationship remains unchanged. The leukemia risk estimate in the regression model with only occupational bone marrow dose (converted from the badge exposure) is slightly higher (OR= 1.11 at 10 mSv; 95%CI= 1.01, 1.22) compared to the model with only occupational badge exposure (OR=1.08 at 10 mSv; 95% CI=1.01, 1.16) because there is less (1,259 mSv) cumulative bone marrow dose than whole body exposure.

There are several possible reasons that the inclusion of work-related medical x-ray exposures made no difference in the leukemia risk estimate despite the fact that medical x-ray exposures were not randomly distributed among the cases and controls (radiation-monitored cases and controls received 2.3 times the work-related medical x-rays of non-monitored cases and controls [Table 4.3.2.A.]). First, these results may provide evidence that the effects produced from work-related medical x-rays are of similar magnitude per unit dose as other occupational radiation exposure. Second, the collective dose contributed from work-related medical x-rays in this study was small compared to badge dose. There was no documentation that PNS ever employed stereoscopic x-ray techniques that were common at Department of Energy (DOE) facilities during the 1940s and 1950s. Therefore, estimates of medical x-ray exposures from photofluorography for PNS workers are lower (1.50 mSv per chest examination) than those estimated in a previous NIOSH study of workers employed at DOE facilities where stereoscopic techniques were used (3.85 mSv per chest examination) (Cardarelli et al., 2002). Also, there was only a narrow window of time (from 1963 through 1968) when radiation-monitored workers received a chest x-ray as part of a yearly radiation qualifying physical examination, and available shipyard records indicate that the use of the photofluorographic x-ray technique for work-related medical x-ray examinations was discontinued at the shipyard after May of 1966 (Daniels et al., 2004b). After May 1966, all work-related medical x-rays used direct radiographic, not photofluorographic, techniques, which dropped average estimated exposures to the active bone marrow from 1.5 mSv per examination to 0.04 mSv per examination.

Overall leukemia mortality was greater among the 374 non-radiation-monitored cases and controls than for the 201 radiation-monitored workers in the study, which is consistent with the findings of the two mortality studies of PNS workers (Rinsky et al., 1988; Silver et al., 2004). As a result there is a substantial change between the radiation exposure coefficient in the unadjusted model that only includes the cumulative radiation exposure variable with a 2 year lag (0.0042) (Table 4.5.1) and the radiation exposure coefficient (0.0082) in the adjusted main effects model (including radiation worker indicator, gender, solvent exposure duration, and three time since last [radiation] exposure categories variables) (Table 4.5.2.B). The radiation worker indicator variable is mainly responsible for the dramatic change in the cumulative dose coefficient because when the radiation worker indicator variable is removed from the main effect model, the parameter estimate for the radiation exposure drops from 0.0082 to 0.0035. Because overall leukemia mortality is greater among non-radiation-monitored workers and the inclusion of the variable makes such a dramatic difference in the radiation exposure coefficient, an analysis including only the 201 radiation-monitored workers in the study was conducted with both log linear and linear ERR models. Gender was dropped from these models because there are no female radiation-monitored workers; the radiation-monitored worker indication variable was also dropped because all workers included in the analysis were radiation-monitored workers.

The final log linear model includes a significant positive exposure-response relationship between disease (leukemia mortality) and exposure (external ionizing radiation), adjusting for solvent

exposure duration; (OR=1.02 at 1 mSv of exposure; 95% CI=1.01, 1.03 and OR=1.20 at 10 mSv of exposure; 95% CI=1.05, 1.37). Solvent exposure duration is elevated but no longer statistically significant (OR=1.05 at one year of exposure; 95% CI= 0.99, 1.10). The final linear excess relative risk model yielded higher risk estimates (RR = 1.04 at 1 mSv; 95% likelihood-based CI=1.01, 1.19; and RR = 1.40 at 10 mSv; 95% likelihood-based CI= 1.05, 2.89) than the log linear model.

5.1. Study Limitations

In evaluating these findings, it is important to consider that the relatively small number of study subjects who were radiation-monitored limited the number of informative cases. However, while the bone marrow doses were increased with the addition of medical x-rays this changed risk estimates very little, suggesting possibly robust findings.

It is also possible that the number of work-related medical x-ray examinations was underestimated for the cases and controls. This is because information about the type and frequency of x-rays was gathered from existing medical records and, although records were available for 90% of the cases and controls, the amount of pertinent information in the medical records varied considerably. This variation was due in part to differences in recording practices by attending physicians and changes in record management policies throughout the years.

To evaluate the impact of work-related medical x-ray exposures on leukemia risk, bone marrow doses from both medical x-rays and occupational exposures were estimated. Many generalizations were required in the development of the dose conversion factors that were applied to cases and controls who received medical x-ray examinations. Therefore, large uncertainties are possible when estimating a particular worker's bone marrow dose, given the variability of several critical parameters over the period of the study. These parameters include, but are not limited to, x-ray procedures and equipment; exposure geometry; incident photon energies; and worker age, sex, and anatomy (Daniels et al., 2004b).

Because the PNS civilian worker cohort and the cases and controls included in this study were overwhelmingly white and male, meaningful analysis of the leukemia risk for either females or non-whites was not possible. However, these results can be generalized to other occupational cohorts that are predominately white and male who received small protracted exposures to low LET (linear energy transfer) radiation.

When comparing the leukemia risk after last exposure in this study with those of individuals included in the Japanese Life Span Study and Russian nuclear workers, it is important to note that the time since last exposed variable in our study is an approximation of the time since exposure variable used in the Life Span and Russian studies. This is because we used the last radiation monitoring date for each of the radiation-monitored cases and controls to define the TSLE variable, while in the other studies, the time since exposure references a single fixed date in time.

Misclassification of workers exposed to the solvents, benzene and carbon tetrachloride is likely. Subjective determinations, based on examination of sparse industrial hygiene data supplemented by field surveys and discussions with Portsmouth Naval Shipyard personnel, had to be used to designate the various shops and jobs with possible benzene and carbon tetrachloride exposure. Efforts were made to reduce misclassification in coding of all work history information by ensuring that all coders were blind to designation of cases and controls.

Also, actual solvent exposure estimates were not known for the cases and controls, necessitating the use of duration of employment in potential solvent-exposed jobs as a surrogate for cumulative solvent exposure estimates. Despite this limitation, there is no evidence of confounding by these solvents of the radiation dose-response relationship observed in this study.

Smoking was not included as a study variable in the analysis because of the lack of readily available individual smoking information in the PNS medical records. There is increasing evidence suggesting that certain forms of adult leukemia; myeloid and acute nonlymphocytic, may be associated with cigarette smoking (Austin and Cole, 1986; Williams and Horm, 1977). However, for diseases such as leukemia that are less related to smoking it is not likely that the increased risk estimate is a result of confounding by smoking (Axelson and Steenland, 1988).

5.2. Conclusions

This study of a workforce exposed to both radiation and known or potential chemical leukemogens provides an estimate of leukemia risk in an occupational context rather than relying on extrapolation from high dose-rate exposures. The findings support other nuclear worker studies that collectively observe slight elevations in leukemia mortality—other than chronic lymphocytic leukemia (CLL)—that appear to be related to increases in low LET radiation exposure (Cragle et al., 1999; Douglas et al., 1994; Schubauer-Berigan and Wenzl, 2001). In the current study, we explored the role of solvent exposures on leukemia risk in greater detail than previous studies involving PNS workers, and observed a significant exposure response between leukemia mortality and the duration of time workers were employed in job categories where solvent exposures were probable.

This case-control study unlike previous PNS studies provides an in-depth analysis of the impact of work-related medical x-ray exposures on leukemia risk using detailed information from worker medical records. The study observed that incorporating dose from work-related medical x-ray exposures had little impact on the radiation-related risk estimate for leukemia in the PNS workers.

The study results reveal information about temporal aspects of the significant radiation exposure response relationship that was observed. The study observed a significant relationship between radiation and leukemia mortality in the ≥ 2.5 year and < 5 years time since last exposure category compared to longer periods. These findings support those of other occupational studies; significant elevations in leukemia risk appear sooner after the last exposure in worker cohorts.

Observation of health risks among individuals in the Japanese Life Span Study did not begin until more than five years after these acute exposures.

5.3. Future Research Directions

Previous studies of nuclear workers and PNS workers have been limited by lower power to detect radiation-related risk due to relatively small numbers of leukemia cases, low radiation exposures, and limited cohort sizes (Schubauer-Berigan and Wenzl, 2001; Rinsky et al., 1988; Stern et al., 1986). To address this issue, studies that combine cohorts of workers for analysis have been and are being conducted; however, differences in radiation exposures and varied dosimetry practices make combined analysis difficult. Because of the similarity of radiological exposures and standardized procedures for monitoring and recording radiological and chemical exposures at all naval shipyards, a combined case-control study of naval shipyards may present a more efficient opportunity for future leukemia studies with more statistical power.

Further research is needed to determine how the rates at which workers receive radiation exposure affect leukemia risk. There have been multiple studies that suggest leukemia incidence is higher among animals subjected to a high dose-rate exposure of low-LET radiation than those subjected to a low dose-rate exposure to low-LET radiation (BEIR V, 1990). Therefore, research leading to the development of methods that can be used in analytic studies to account for the effects of dose-rate on leukemia risk would be desirable.

Currently, there are few occupational radiation studies that attempt to control for possible chemical leukemogens such as benzene or other solvents. Despite the fact that chemical exposure assessments are complex for large cohorts of workers and exposure records are sparse, continued research toward the development of methods to estimate the joint effects of workplace exposures such as solvent and radiation exposure are needed.

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Appendix A

1. Definition and Description of Leukemia

Leukemia is the name used to describe a variety of hematologic (related to blood and blood-forming organs) malignancies that begin in the blood-forming cells of the bone marrow. When leukemia occurs, the body produces too many abnormally immature blood cells. In most leukemias, the abnormally immature blood cells produced are white blood cells (leukocytes); however, abnormal numbers of immature red blood cells (erythrocytes) and platelets (thrombocytes) may also occur. Major symptoms of leukemia include infections due to a decrease in normal white blood cells, anemia due to a decrease in normal red blood cells, and excessive bleeding due to a decrease in normal platelets. Leukemias are classified by form as either acute or chronic (characterizes how quickly the disease develops), and by type, either myeloid or lymphoid (characterizes the type of blood cell that is primarily affected) (Wujcik, 1992; Riddon, 1995).

1.1. Acute and Chronic Leukemias

The acute form of leukemia is characterized by a rapid increase in the number of immature blood cells that remain immature and are unable to perform their normal function, resulting in a short survival time without immediate medical intervention. Acute leukemia is often difficult to diagnose because the symptoms (fever; flu-like symptoms; changes in energy level, appetite and temperament; joint or bone pain; and tendency to bruise or bleed easily) are often vague and present for a short period of time (less than three months). The chronic form of leukemia usually progresses more slowly than acute leukemia. Unlike the immature cells that characterize acute leukemia, the predominant cell characterizing chronic leukemia appears mature, but does not function normally. Chronic leukemia usually has a gradual onset, prolonged clinical course, and a relatively longer survival time (Wujcik, 1992; Riddon, 1995).

1.2. Myeloid and Lymphoid Leukemias

The bone marrow, which is the soft material that fills the cavities of the bones, is where adult blood cells are produced. There are two blood cell lines produced by the bone marrow, the myeloid and lymphoid cell lines, which are involved in blood cell production. The myeloid cell line includes cells that mature into erythrocytes (red blood cells), thrombocytes (platelets), and some leukocytes (white blood cells). The white blood cells from the myeloid cell line include macrophages (which ingest foreign particles), eosinophils (which trigger allergies), and neutrophils (which protect against bacterial infections). The lymphoid cell line includes both T-cell (released from the thymus gland) and B-cell (released from the bone marrow) lymphocytes, which produce antibodies that attack foreign substances in the body. Leukemia is a disease that is characterized by an interruption in the maturation of either the myeloid or lymphoid cell line causing production of ineffective blood cells that are unable to function correctly (Seeley et al., 2002; Wujcik, 1992).

2. Identification of Leukemia as a Clinical Entity—A Brief History

There is no evidence in the medical literature that would suggest that leukemia had been identified or described before the 19th century (Piller, 2002). It is thought that A. Velpeau provided the first accurate description of a leukemia case in 1827. He was treating a 63-year-old patient who became ill in 1825 with fever, weakness, and swelling of the abdomen. The patient died soon after admission to the hospital and the autopsy revealed that he had a severely enlarged liver and spleen. His blood contained colorless corpuscles and appeared thick “like gruel...resembling in consistency and color the yeast of red wine” (Gunz, 1985; Piller, 2002). It was this peculiar characteristic of the blood which first attracted early observers such as Rudolph Virchow, a German pathologist, who first introduced the term leukemia in 1847 to describe this unusual appearance of the blood (Gunz, 1985).

In 1856, Virchow published a summary of a series of studies he conducted examining the pathology of leukemia. These remarkable studies provided several important insights into the pathology of leukemia that are still relevant today, and were made when little knowledge existed on the sites and mechanisms of hematopoiesis and on the function of the blood cell. First, he explained that the colorless corpuscles he had observed are always present in normal blood and that their increase does not necessarily indicate the presence of leukemia. Second, he described leukemia as a clearly defined pathologic state characterized by not only an increase in “colorless cells, but also a decrease in the number of red corpuscles.” Third, he explained that some patients exhibited enlargement of the lymph nodes or spleen months or even years before changes developed and were observed in the blood. He concluded that changes in the organs of leukemia patients precede those in the blood (Gunz, 1985).

Following the work of Virchow, there were several other important 19th century discoveries related to leukemia. In 1870, Newman demonstrated that the bone marrow is an important site for the formation of blood corpuscles. This discovery was followed in 1879 by Gower’s report that anemia in leukemia patients may be caused by either diminished formation of red blood cells or by their excessive destruction. In 1889, Ebstein was the first to describe acute leukemia as a distinct clinical entity. Franke’s report soon followed in which revealed in 1895 acute leukemia is more common than chronic leukemia. By the end of the nineteenth century, much progress had been made in establishing a clear definition and classification of subtypes of leukemia, however, these advancements provided little help in advancing the treatment of the disease (Piller, 2001).

3. Leukemia Treatment—A Brief History

Attempts were made to treat leukemia soon after the disease was identified, but all proved to be unsuccessful. It was not until 1865—some 38 years after Velpeau provided the first description of leukemia—that the first leukemia remission was reported in a patient with chronic granulocytic leukemia. The patient had been treated with a tonic that contained arsenious oxide. After this remission was reported, arsenic became the standard treatment for chronic leukemia for the next 30 years (Gunz, 1985). The next advance in the treatment of chronic leukemia occurred in 1902, when x-rays (discovered by Rontgen in 1895) were found to be effective in treating chronic leukemias. Like arsenic, however, x-rays proved to be ineffective for treating acute leukemia, and offered only temporary relief and no cure for chronic leukemia (Gunz, 1985).

In 1910 it was discovered that the organic solvent benzol is destructive to blood cells. For this reason, it was used to treat leukemia. Its toxic effects were so severe and unpredictable however, that it was widely used for only about 10 years. Until the 1940s, treatment was limited to x-ray therapy for chronic leukemia, which provided only symptomatic relief, not a cure (Gunz, 1985). Acute leukemias continued to be non-responsive to any type of intervention. During World War II, while research was being conducted on the military uses of mustard gas, it was discovered that nitrogen mustards are a strong bone marrow depressant. Furthermore, clinical trials conducted in secrecy during World War II on patients with advanced Hodgkin's disease, lymphosarcomas, and leukemia revealed that these agents could induce excellent remissions of lymphomas, although their antileukemic activity was limited (Gunz, 1985).

The results of these clinical trials were published after the end of World War II in 1946, in the *Journal of the American Medical Association* (Goldman, et al., 1946; Jacobson, et al., 1946). Also in 1946, Gillman and Philips published a study indicating that the effects from the nitrogen mustards in the treatment of leukemia closely resembled those from x-rays (Gilman and Philips, 1946). These published findings stimulated further research into the development of other therapeutic chemical agents that were used to treat primarily chronic leukemia. Between 1946 and 1956, several compounds were synthesized in the United States and Great Britain including triethlenemelamine, busulfan, and chlorambucil, which became known collectively as the alkylating agents. Unlike nitrogen mustards, they could be taken by mouth, but their acute toxicity to the bone marrow and other tissues was pronounced (Gunz, 1985).

None of the new chemical agents however, were effective in treating acute leukemia. Significant progress in treating acute leukemia did not occur until the mid-1950s, when Dr. Sidney Farber of Boston first used the folic acid antagonist aminopterin to treat 16 children with acute leukemia. Farber reported that although aminopterin was extremely toxic, 10 of 16 children with acute lymphocytic leukemia (ALL) who were treated with it achieved a temporary remission. This finding provided new hope that effective treatment of acute leukemia was possible. Current standard leukemia treatment regimens produce remission in approximately 70% of adults with

ALL, and long-term survival rates averaging approximately 40%. Current treatment has also improved long-term survival for adults with chronic lymphocytic leukemia (CLL); however, current long term survival remains very low for both acute myeloid leukemia (AML) (20%) and chronic myeloid leukemia (CML) (25%) (Borson and Loeb, 1994).

4. Leukemia Mortality in the United States

4.1. Mortality from All Leukemia Types Combined—Trends for Males and Females, All Races

The American Cancer Society (ACS) estimates that there will be 21,700 leukemia deaths [12,100 (56%) males and 9,600 (44%) females] in the United States in 2002. Since the 1960s, there has been a significant decrease in childhood leukemia mortality in the United States among both white and nonwhite children due primarily to therapeutic treatment advances (The American Cancer Society, 2002). Adults have not experienced a similar decline in mortality. According to information from the National Cancer Institute, the age-adjusted leukemia mortality for both adult men and adult women gradually increased from 1950 to 1972, (Appendix B, Tables 1 & 2). This increase was due primarily to increases among elderly non-white adults (Linnet and Cartwright, 1996; The American Cancer Society, 2002; Ries et al., 2002). Between 1973 and 1999, however, leukemia mortality for both adult men and women declined slightly (Ries et al., 2002).

4.2. Mortality from All Leukemia Types Combined—Trends for Males of All Races

According to data provided by the National Center for Health Statistics (NCHS) between 1973 and 1999, the age-adjusted mortality for all leukemias among males of all races gradually declined. The decline was most pronounced from 1995 to 1998, during which time the rates decreased from 10.8 per 100,000 to 10.1 per 100,000 (Appendix B, Table 3) (Ries et al., 2002).

4.3. Mortality from All Leukemia Types Combined—Trends for Females of All Races

The age-adjusted mortality for all leukemia types combined is lower for females than for males. According to the NCHS, the age-adjusted mortality among females of all races gradually decreased from 1973 to 1998. The combined female rates reached a high of 6.5 per 100,000 in 1980, and a low of 5.9 per 100,000 in 1998 (Appendix B, Table 4) (Ries et al., 2002).

4.4. Mortality from All Leukemia Types Combined—Trends for White Males and Females

The age-adjusted mortality for white males from all leukemia types combined has slowly increased from 1973 to 1980, reaching a high of 11.5 per 100,000 in 1980 (Appendix B, Table 5). The rates declined slowly from 1981 to 1987, followed by a more pronounced decline from

1995 to 1998, when rates fell from 11.0 per 100,000 in 1995 to 10.3 per 100,000 in 1998. The age-adjusted mortality for white females is lower than that for white males and has also declined slowly from 1980 to 1999, reaching a high of 6.6 per 100,000 in 1980 and a low of 6.0 per 100,000 in 1998 (Ries et al., 2002).

4.5. Leukemia Mortality for All Leukemia Types Combined—Black Males and Females

The age-adjusted mortality for all leukemia types combined for black males is lower than for white males and gradually increased from a low of 8.2 per 100,000 in 1973 to a high of 10.3 per 100,000 in 1989. It then decreased gradually from 1989 to 1999 (Appendix B, Table 5). The age-adjusted mortality for black females for all types of leukemia combined, which is lower than for white or black males and white females, increased from 1973 to 1981 and then declined gradually from 1982 to 1997 (Appendix B, Table 5) (Ries et al., 2002).

5. Leukemia Incidence in the United States

5.1. Incidence of All Leukemia Types Combined

The American Cancer Society estimates that there will be 30,800 new cases of leukemia diagnosed in the United States in 2002 [17,600 (57%) males and 13,200 (43%) females]. Acute and chronic types of leukemia are projected to occur in approximately equal proportions in these new cases. Incidence rates are highest among white males and lowest among black females (The American Cancer Society, 2002).

5.2. Incidence of All Leukemia Types Combined—Trends for White Males and Females

According to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) data base, age-adjusted leukemia incidence rates among white males have remained stable from 1973 through 1995, when they began to decrease (Appendix B, Table 5). Age-adjusted incidence rates among white females have also remained stable from 1973 through 1995, after which they began to decline (The National Cancer Institute, 2002; Ries, 2002).

5.3. Incidence of All Leukemia Types Combined—Trends for Black Males and Females

The age-adjusted incidence rates for black men and women have shown more variation than the rates for white males and females; however, incidence rates for both groups have been decreasing since 1973 (Appendix B, Table 5) (Ries et al., 2002).

5.4. Survival Rates for All Leukemia Types Combined—Both Males and Females

Currently, the one-year survival rate for males and females of all races with leukemia is 63.5%, while the five-year survival rate decreases to 46.4%. This decrease is due in part to the poor survival rate of individuals with acute myeloid leukemia. The five-year survival rates for all types have improved since the early 1960s (Table 5.4); however, there is still no known cure for leukemia (Ries et al., 2002).

6. The Four Major Leukemia Subtypes—Incidence, Mortality, and Five-Year Survival Rates

6.1. Acute Myeloid Leukemia (AML)

The American Cancer Society estimates that there will be 10,600 new AML cases diagnosed in 2002 [5,900 (56%) males and 4,700 (44%) females] (The American Cancer Society, 2002). The incidence rates for AML increase dramatically among adults over the age of 40; it is the most common form of leukemia among older adults and is most prevalent in the sixth, seventh, and eighth decades of life (The American Cancer Society, 2002). The incidence of AML is less than 1/100,000 among individuals younger than 35 years of age and rises dramatically for individuals older than 60 years of age (especially white males) (Appendix B, Table 6). The American Cancer Society estimates that 7,400 deaths [4,000 (54%) male and 3,400 (46%) female] will result from AML in 2002. Mortality rates rise sharply after age 50, particularly for white males (Appendix B—Table 7). Currently, the five-year survival rate for adults with AML who achieve a complete remission following chemotherapy is approximately 25% (The American Cancer Society, 2002; Ries et al., 2002).

6.2. Chronic Lymphocytic Leukemia (CLL)

CLL is the second most common form of adult leukemia and 90% of the new cases are diagnosed in individuals who are older than age 50 (Appendix B, Table 8) (Reis et al., 2002). It is estimated that 7,000 new cases [4,100 (59%) male and 2,900 (41%) female] will be diagnosed in 2002 and that 4,500 deaths [2,600 (58%) male and 1,900 (42%) female] will result from CLL in 2002. Mortality rates rise sharply after age 60, particularly for white and black males (Appendix B—Table 9). Currently, the overall five-year survival rate for adults with CLL is approximately 60% (The American Cancer Society, 2002; Ries et al., 2002).

Table 5.4. Changes in the Five Year Survival Rates for All Leukemia Types Combined: from the National Cancer Institute (Ries et al., 2002)

Year of Diagnosis	Whites (Male and Female)	Blacks (Male and Female)
1960–1963	14%	Not available
1970–1973	22%	Not available
1974–1976	35.2%	31.2%
1977–1979	38.0%	30.4%
1980–1982	39.5%	32.9%
1983–1985	42.0%	33.6%
1986–1988	44.2%	38.0%
1989–1991	45.8%	34.1%
1992–1998	47.3%	38.4%

6.3. Chronic Myeloid Leukemia (CML)

It is estimated that there will be 4,400 new cases [2,500 (57%) males and 1,900 (43%) females] of CML diagnosed in 2002. CML incidence also rises with age (Appendix B, Table 10), and the overall five-year survival rate for CML is approximately 32%. It is estimated that 2,000 deaths [1,100 (55%) males and 900 (45%) females] will result from CML in 2002. Mortality rises dramatically for white and black males and females after age 60; however, the rise after age 60 is most pronounced for white males (Appendix B, Table 11) (The American Cancer Society, 2002; Ries et al., 2002).

6.4. Acute Lymphocytic Leukemia (ALL)

ALL accounts for 78% of childhood leukemias but only 5% of leukemias in adults older than 40 years of age. Age-specific patterns in the United States show a peak among children ages 2–4, with a decline in rates to a low at ages 25–59, followed by an increase to a second, slightly lower peak at ages 85 and older (The American Cancer Society, 2002). It is estimated that 3,800 new adult ALL cases [2,200 (58%) males and 1,600 (42%) females] will be diagnosed in 2002. Incidence rises most dramatically among white males after age 70 (Appendix B, Table 12). The overall five-year survival rate is approximately 40%, and it is estimated that there will be 1,400 adult deaths [800 (57%) male and 600 (43%) female] from ALL in 2002. Mortality rises dramatically for blacks and whites of both sexes after age 60 (Appendix B, Table 13) (The American Cancer Society, 2002; Ries et al., 2002).

7. Risk Factors

7.1. General

The exact cause of leukemia is not yet known. However, leukemias are associated with certain environmental, occupational, and genetic risk factors. Primary occupational risks include exposure to ionizing radiation (BEIR V, 1990; Cardis et al., 1995; Cardarelli et al., 2002) and benzene (Proctor and Hughes, 1996; Vigliani, et al., 1976; Rinsky et al., 1981; Bond et al., 1986; Rinsky et al., 1987). Non-occupational risks include diagnostic x-rays (Evans et al., 1986), radiation therapy (Curtis et al., 1984; Boice et al., 1987), alkylating chemotherapy drugs (Ruddon 1995), and smoking (Austin et al., 1986; McLaughlin et al., 1989; Brown et al., 1992; Kabat et al., 1988; Brownson et al., 1993). Additional associations have been noted with familial and genetic disorders, and chromosomal syndromes (including Down, Klinefelters's, and Bloom's syndromes) (Mitus et al., 1995; Ruddon, 1995; Klassen, 1996).

7.2. Familial and Genetic Factors

Beginning in the 1940's, evidence of a relationship between genetic factors and the incidence of leukemia—especially chronic lymphocytic leukemia (CLL)—began to emerge from case-control and case-series studies examining the incidence of leukemia among family members (Schweitzer, 1973; Gunz, 1966; Fraumeni et al., 1969; Linet, 1989; Finch and Linet, 1992;

Cuttner, 1992). A case-control study conducted by Videbaek in 1947 was the first to suggest an increased incidence of all forms of leukemia among relatives of leukemia patients (Videbaek, 1947; Gunz and Veale, 1969). Videbaek's findings were not confirmed in subsequent studies in the 1950s and early 1960s and were criticized on both methodological and statistical grounds (Gunz, 1966; Steinberg, 1960; Busk, 1948). However, three case-survey studies conducted from the mid-1960s and 1970s with a combined total of 1500 families (Gunz, 1964; Gunz and Veale, 1969; Gunz et al., 1975) did support the findings reported by Vidabaek. These studies reported that the familial incidence of leukemia is nearly three times higher than expected among relatives of leukemia patients, and that the incidence of a second case is higher among first-degree relatives (parent, sibling, and child) than more distant relatives. They also reported that the risk of familial leukemia appears to be greatest among relatives of patients with CLL, while less so among relatives of patients with acute leukemias. (Gunz, 1964; Gunz and Veale 1969; Gunz et al., 1975; Gunz, 1977; Cuttner, 1992).

Some case-control studies have reported excess leukemia among family members of cases, supporting the findings reported by Vidabaek in 1947 and subsequent case-series studies (Cartwright, 1987; Linet, 1989; Pottern, 1991). Pottern, in a case-control study that included 578 leukemia cases, reported that a history of stomach cancer in either parent and prostate cancer in fathers was associated with a two-fold elevation in the incidence of CLL (Pottern, 1991).

7.3. Chromosomal Syndromes

An elevated risk of leukemia has been reported among children with certain hereditary and congenital conditions that are accompanied by chromosomal instabilities (Linet and Cartwright, 1996). Multiple studies have reported that children with Down syndrome have a 20- to 30-fold increased incidence of acute leukemia of various cell types, compared to the general population (Epstein and McCoy, 1987; Fong and Brodeur, 1987; Zack et al., 1991). Narod, in a survey of 16,564 cases of childhood cancer diagnosed in Great Britain from 1971 to 1983, reported that Down syndrome was diagnosed in more than 90% of the children who had both a genetic disorder and leukemia (Narod et al., 1991). The age of onset for leukemia in children with Down syndrome is bimodal, peaking first in the newborn period and again at 3–6 years. This increased risk extends into adulthood. (Fong and Brodeur, 1987)

Other disorders with chromosomal abnormalities or fragilities associated with leukemia include the following: Klinefelter's syndrome, which is seen in approximately 1/1000 male births and is a condition characterized by small testes and atrophy of the seminiferous tubules. It is associated most often with AML. (Jorde, 1999). Bloom syndrome is characterized by permanent dilation of facial blood vessels, creating small focal red lesions, photosensitivity, and dwarfism (of prenatal onset) (Jorde, 1999). It is associated with a significant increase in ALL in younger individuals and AML in older individuals (Linet and Cartwright, 1996). Fanconi's anemia is characterized by pancytopenia (deficiency of all cell elements of the blood) and underdevelopment of the bone

marrow. It is estimated that 10 - 20% of individuals with this disorder develop AML (Linnet and Cartwright, 1996).

In general, the factors responsible for the chromosome changes in individuals with leukemia are unknown, although chromosomal abnormalities in a few cases have been linked to exposure to ionizing radiation, benzene, other solvents, pesticides, or to treatment with certain types of chemotherapy drugs. It is not known if chromosomal defects cause or just coexist with leukemia; however, presence of chromosomal abnormality and/or fragility appears to favor progression to a malignant state (Linnet and Cartwright, 1996).

7.4. Viruses

7.4.1. HTLV – Types I and II

Since 1980, the Human T-Lymphotropic Type 1 Virus (HTLV-1) has been established as the primary etiologic factor in adult T-cell leukemia-lymphoma (Blattner, 1993; Linnet and Cartwright, 1996). Adult T-cell leukemia (ATL) is an aggressive form of leukemia difficult to distinguish from CLL, that is uniformly fatal (CDC, 1993). Transmission of HTLV-1 occurs prenatally from mother to child, or through sexual contact, blood transfusion, or sharing contaminated needles. In the United States, most of those infected report either birth in endemic countries (southwest Japan, the Caribbean basin, Melanesia, and Africa) or sexual contact with a person from an endemic country (CDC, 1993).

The Human T-Lymphotropic Type II Virus (HTLV-II) infection was first isolated from two patients with hairy-cell leukemia (CLL variant) in 1982. However, currently the infection is not clearly associated with hairy-cell or any other types of leukemias (Kalyanaraman et al., 1982; CDC, 1993).

7.4.2. Epstein-Barr Virus

The Epstein-Barr virus is a member of the herpes virus family and one of the most common human viruses (Linnet and Cartwright, 1996). Case report studies have associated the virus with a lymphoproliferation terminating in acute lymphocytic leukemia (ALL) (Finlay et al., 1986) or chronic myeloid leukemia (CML) (Mecucci et al., 1986; Linnet and Cartwright, 1996).

7.4.3. Hepatitis B Virus

Hepatitis B is a viral disease caused by the hepatitis B virus that is endemic worldwide. It is characterized by hepatic cell destruction leading to anorexia, jaundice, and hepatomegaly (enlargement of the liver). In most cases, the hepatic cells regenerate and individuals recover (Taylor, 1988). The hepatitis B virus has been found in the hemopoietic cells of adults with AML prior to treatment with blood transfusions (Linnet and Cartwright, 1996). In a study of 51 children diagnosed with leukemia, Pontisso et al., reported that 55% with myeloid leukemia tested positive for hepatitis B prior to receiving any transfusion therapy (Pontisso, et al., 1987; Linnet and Cartwright, 1996).

7.5. Cigarette Smoking

An association between cigarette smoking and leukemia was not reported until the mid- 1980s, decades after the association between smoking and lung cancer was first established in 1950 (Linnet and Cartwright, 1996). In 1976, a 20-year follow-up of 34,440 British doctors who replied to a questionnaire about their smoking habits failed to find an increase in leukemia among smokers (Doll and Peto, 1976). The 1982 United States Surgeon General's Report on the Health Consequences of Smoking reported that while cigarette smoking is a major cause of cancers of the lung, larynx, oral cavity, and esophagus, leukemia is not considered a tobacco-related cancer (U.S. Department of Health Services, 1982).

In 1986, in a review of several leukemia cohort and case-control studies, Austin and Cole suggested that sufficient epidemiological evidence existed to provide some support for the inference that cigarette smoking is a risk factor for leukemia (Austin and Cole, 1986). They noted that a 1977 case-control study that included 172 leukemia incident cases identified from the third National Cancer Survey Tumor Registry reported an increased risk of all leukemia (RR = 1.89; 95% CI 1.38, 2.5) and an increased risk of myeloid leukemia (RR = 2.09; 95% CI 1.18, 3.71) (Austin and Cole, 1986; Williams and Horm, 1977). They also cited a 1978 case-control study by Paffenbarger et al., of male Harvard and University of Pennsylvania alumni that included 96 lymphatic and myeloid leukemia deaths. They reported a statistically significant increased risk of all leukemias (RR = 1.7; 95% CI 1.1, 2.7), and myeloid leukemia (RR = 2.3; 95% CI 1.1, 4.6) but not of lymphatic leukemia (RR = 1.3; 95% CI 0.5, 3.2) (Austin and Cole, 1986; Paffenbarger, 1978; Siegle, 1993).

Garfinkel and Boffetta conducted two American Cancer Society prospective cohort mortality studies that included 1,387 leukemia deaths. They reported a positive association between myeloid leukemia and smoking in men in both studies (SMR = 2.44 and 1.32; $p < 0.05$) but not with smoking among women. They also reported no elevation in lymphatic leukemia mortality risk among men and women in both studies (Garfinkel and Boffetta, 1990). A meta-analysis of seven cohort and eight case-control studies published from 1970 to 1992 was conducted by Brownson et al., in 1993. They reported that the cohort study data suggested an elevated risk of myeloid leukemia associated with cigarette smoking (RR = 1.4; 95% CI 1.2, 1.6) and that the case-control study data suggested an elevated risk of acute nonlymphocytic leukemia with cigarette smoking (RR = 1.3; 95% CI 1.1, 1.5) (Brownson et al., 1993). In a 1993 review article, Siegel reported that most of the fifteen studies he reviewed supported an association between myeloid leukemia and smoking. He also reported that there is insufficient information to rule out a possible association between smoking and lymphatic leukemia or between acute and chronic leukemia types (Siegel, 1993). It is thought that constituents such as benzene found in tobacco smoke may be responsible for the increased risk of leukemia among smokers (Linnet and Cartwright, 1996).

7.6. Solvent Exposure

7.6.1. Benzene

Benzene was first isolated from coal tar Naphtha by Faraday in 1825. It is used for the manufacturing of some types of rubber, lubricants, dyes, and pesticides. Natural sources of benzene include volcanoes and forest fires. It is also a part of crude oil and cigarette smoke (Hunter, 1975; ATSDR, 1997). Delore and Borgomano described the first case of acute leukemia among benzene-exposed workers in 1928 (Rinsky et al., 1987). Since 1928, numerous studies have reported excess incidence of leukemia among workers employed in shoe, chemical, and rubber manufacturing, where exposure to benzene occurred. In 1989, Paci reported significantly elevated levels of mortality from acute leukemia among both men and women employed at a shoe manufacturing plant in Italy, which used adhesives that were prepared with benzene (Paci et al., 1989). In 1981, the National Institute for Occupational Safety and Health (NIOSH) conducted a retrospective cohort mortality study of 748 rubber workers exposed to benzene during the production of rubber hydrochloride at two Ohio facilities. The workers included in the study were exposed to benzene for at least one day between 1940 and 1950. The NIOSH researchers reported a five-fold excess risk of death from all types of leukemia combined and a ten-fold excess risk of death from myeloid and monocytic leukemias combined. They also reported that the duration of exposure to benzene was brief and 58% of the cohort was exposed for less than one year (Rinsky et al., 1981). The findings of these studies were instrumental in the decision by the International Agency for Research on Cancer (IARC) to recognize benzene as a cause of AML in humans (IARC, 1981).

Subsequent cohort mortality studies of workers employed in chemical manufacturing and oil refineries and exposed to benzene in the United States (Wong, 1987; McCraw, 1985), the United Kingdom (Rushton and Alderson, 1981), and China (Yin et al., 1987) have also reported excess leukemia deaths among benzene-exposed workers.

7.6.2. Carbon Tetrachloride

Carbon tetrachloride has been used in the manufacture of fluorocarbon propellants, as a solvent for oils, fats, lacquers, varnishes, rubber waxes, and resins; as a degreasing and cleaning agent; and as a fumigant to kill insects in grain (Proctor and Hughes, 1996; ATSDR, 1994). Lynge et al. conducted a review of the epidemiological evidence on the relationship between organic solvents and cancer. They reported that there is some evidence of excess risk of lymphohematopoietic malignancies among workers exposed to carbon tetrachloride (Lynge, 1997). Wilcosky et al. analyzed the effect of multiple solvent exposures among a 6,678-member cohort of workers employed at a rubber and tire manufacturing plant. They conducted a case-control study comparing the exposure histories of a 20% age-stratified random sample of the cohort with the exposure histories of cohort members who died between 1964 and 1973 from stomach cancer, respiratory system cancer, prostate cancer, lymphosarcoma, and lymphatic leukemia. They reported that lymphatic leukemia was strongly related to carbon tetrachloride (OR= 15.3; $p < 0.0001$) and carbon disulfide (OR = 8.9; $p = 0.0003$) exposure (Wilcosky et al., 1984;

Checkoway et al., 1984). Neither carbon tetrachloride nor carbon disulfide has been shown in other studies to be leukemogenic (Checkoway et al., 1984). The International Agency for Research on Cancer (IARC) has reported that there is sufficient evidence to conclude that carbon tetrachloride is an animal carcinogen, and inadequate evidence to support a conclusion that it is a human carcinogen (IARC, 1995).

7.6.3. Ethylene Glycol

Ethylene glycol is a solvent used in the paint and plastics industry. It is also used to make antifreeze and de-icing solutions for cars, airplanes, and boats (ATSDR, 1997). There are no studies to date that report an association between ethylene glycol and leukemia. However, Welch and Cullen conducted a study examining the effect of exposures to ethylene glycol ethers among a group of 73 shipyard painters and 40 controls. They reported that significant portions of the painters were anemic (10%) and granulocytopenic (5%), while none of the controls were affected (Welch and Cullen, 1988).

7.6.4. Styrene and Butadiene

Studies conducted primarily during the 1970s and 1980s first suggested a possible increased risk of lymphohematopoietic cancers among rubber industry workers exposed to styrene and butadiene (Lynge et al., 1997). However, excess leukemia among workers occupationally exposed to styrene and butadiene has not been reported consistently. McMichael et al. conducted a mortality study of 6,678 males employed at a single rubber manufacturing plant where styrene monomers and butadiene were processed. The study examined associations between specific causes of death and a history of having worked in certain job categories within the plant. They reported that lymphatic leukemias were significantly associated with solvent-exposure job categories such as finishing and repair (McMichael et al., 1976). In 1982, Meinhardt et al. conducted a mortality study of 2,756 workers employed at two styrene-butadiene rubber producing plants and reported a non-statistically significant elevation in leukemia mortality (Meinhardt et al., 1982). An update of this cohort completed in 1990 reported a small increase in leukemia mortality. The increase in leukemia mortality however, appeared among workers with smaller but not longer duration of solvent exposure. This finding appears inconsistent with a causal association (Lemen, 1990).

A cohort mortality study of 12,110 male workers employed for at least one year in eight styrene-butadiene polymer manufacturing plants in the United States and Canada and followed for vital status from 1943 through 1982 reported no excess in leukemia mortality (Matanoski et al., 1990). Also, a meta-analysis that included 17,448 workers with an average follow-up of 22 years conducted by Cole et al. in 1993 found little evidence of excess leukemia risk among workers exposed to styrene and butadiene (SMR = 1.05; 95% CI .74, 1.46) (Cole et al., 1993).

A Danish cancer-incidence study that included 36,610 workers of 386 reinforced plastics companies and 14,293 workers not exposed to styrene from similar industries reported an

increased excess risk of leukemia (SIR = 1.54; 95% CI, 1.04, 2.19) among individuals employed in the 1960s. During this period (which was the period of highest recorded styrene levels), the average recorded exposure level was 767 mg/m³ (Kolstad et al., 1994, Lynge et al., 1997).

7.7. Ionizing Radiation—Atomic Bomb Exposures

7.7.1. Japanese Atomic Bomb Survivors

The United States government, under the auspices of the National Academy of Sciences, established the Atomic Bomb Casualty Commission (ABCC) in Hiroshima and Nagasaki in 1947 and 1948, respectively. The ABCC, which was reorganized in 1975 into the Radiation Effects Research Foundation (RERF), established the Life Span Study (LSS) in 1950 to study the health effects on individuals who were exposed to atomic bomb radiation (Shigematsu, 2000). Subjects included in the LSS included atomic bomb survivors who were residing in Hiroshima or Nagasaki at the time the first nationwide survey of survivors was conducted in 1950. The LSS study population of 120,128 individuals includes 91,228 individuals exposed to radiation, 26,517 who were not in either city at the time of the bombing, and 2,383 individuals for whom a radiation dose could not be estimated (Shimizu et al., 1990). Through 1990, the LSS has documented 249 leukemia deaths from approximately 2,735,335 person-years of follow-up (Pierce et al., 1996). Approximately 55% of the leukemia occurrence among the survivors from 1950 through 1985 was attributable to radiation exposure from the bombs. This is a proportion far greater than estimated for other cancers (Shimizu et al., 1989; Linet and Cartwright, 1996). The LSS reported that mortality is significantly elevated for acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and acute lymphoblastic leukemia (ALL). For individuals who were under the age of 30 at the time of the bomb detonation, ALL is the most prevalent type of leukemia. AML is the most prevalent for those who were age 45 and older at the time of the bomb blast (Shimizu et al., 1989). Mortality from CML peaked within five years of exposure and the relative risk of developing CML was greater in younger individuals (younger than 15 years of age at the time of the bomb blast) than in older individuals (Linet and Cartwright, 1996). The study also demonstrated that the younger a person was at the time of the blast, the greater the risk of leukemia in the first few years after the blast and the more rapid the decline in risk in later years (BEIR V, 1990). The LSS has not shown an association with chronic lymphocytic leukemia (CLL), however; this could be due to the very low background rates of CLL among the Japanese (UNSCEAR, 2000).

7.7.2. Military Personnel Present During Nuclear Weapons Testing

Epidemiologic studies of military personnel who were present at several above-ground nuclear tests have shown conflicting results with respect to leukemia risk (Schubauer-Berigan and Wenzl, 2001). A 1979 Centers for Disease Control and Prevention (CDC) report indicated that military personnel who participated in the 1957 above-ground nuclear test in Nevada (SMOKY) had an excess of leukemia cases when compared to individuals of the same age and sex in the general population (CDC, 1979). A follow-up study of this cohort in 1983 reported no excess in total cancer among 3,017 of the 3,217 military participants. Leukemia was the only cancer that

was significantly elevated. The study reported a 2.5-fold increase in leukemia, primarily AML and CML, among individuals with cumulative gamma radiation exposures (measured by individual film badges) that ranged from 0–10,397 mrem (Caldwell, 1983; Watanabe, 1995, Linet and Cartwright, 1996). Leukemia mortality however, has not been elevated in other cohorts of military personnel involved in other above-ground tests. A 1985 survey by Robinette et al., of 46,186 military personnel who participated in two above-ground tests at the Nevada Test Site (NTS) and three in the Pacific Ocean reported no excess of non-leukemia deaths. Excluding the 1957 (SMOKY) test, the survey reported 46 leukemia deaths vs. 52.4 expected (Boice and Inskip, 1996). It is possible that the leukemia excess among SMOKY participants was due to chance or circumstances peculiar to that test (Boice and Inskip, 1996; Linet and Cartwright, 1996).

A mortality study of British military and civilian personnel who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programs was conducted by Darby et al. in 1994. The study which included 21,358 military and civilian personnel reported no excess mortality due to leukemia or multiple myeloma (Darby et al., 1993).

7.8. Ionizing Radiation—Occupational Studies of United States, British, and Russian Nuclear Workers

During the past 25 years there have been multiple studies examining the association between leukemia and ionizing radiation among workers employed in a variety of areas of the nuclear industry in the United States, Great Britain, and the former Soviet Union. British cohorts are often smaller and the exposures in some British cohorts are greater than many of those in U.S. studies. While several important studies of leukemia and other cancers have been conducted in the former Soviet Union, these cohorts of nuclear workers have much higher radiation exposures than either the U.S. or British cohorts (Schubauer-Berigan and Wenzl, 2001).

7.8.1. The United States Department of Energy Hanford Facility

The Hanford Facility was established in 1942 on 360,000 acres in southeast Washington State. During its operation, the primary functions of the plant included the fabrication of nuclear reactor fuel, the operation of nine nuclear reactors and five isotope separation facilities, and the fabrication of plutonium components for nuclear weapons (U.S. Department of Energy, 1997). There have been several large cohort mortality studies of Hanford workers since the late 1970's that have examined an association between ionizing radiation exposure and leukemia mortality (Schubauer-Berigan and Wenzl, 2001). A 1977 mortality study conducted by Mancusco et al. of 24,939 male workers employed from 1944 through 1972 reported that workers who died of leukemia and other lymphatic neoplasm's had received higher cumulative radiation doses compared to workers who died of other cancers and non-cancers (Mancusco, 1977). A re-analysis of the data used in the Mancusco study was done by Hutchinson et al. in 1979. They conducted the analysis while adjusting for age and calendar year of death which reduced the number of cancer sites exhibiting a dose response relationship with radiation. They reported no

relationship between lymphatic and hematopoietic cancers other than myeloma (Hutchinson et al., 1979). Several other studies have reported no association between radiation exposure and leukemia among Hanford workers. Gilbert and Marks conducted a mortality study of 12,522 radiation-monitored white male workers employed at Hanford for at least two years from 1944 through 1965, with vital status follow-up through 1974. They reported no excess leukemia mortality among the workers, and no association between leukemia mortality and levels of radiation exposure (Gilbert and Marks, 1979). In 1993, Gilbert, et al. reported no excess leukemia mortality among 32,643 male and female radiation-monitored Hanford workers employed for at least six months from 1944 through 1978. They also reported no positive association between cumulative radiation exposure and leukemia mortality among these workers (Gilbert et al., 1993).

7.8.2. The United States Department of Energy Savannah River Plant

The Savannah River Plant is located on 192,000 acres, approximately 13 miles south of Aiken, South Carolina. The facility was built in the early 1950's and its primary purpose was to produce, purify, and process radioisotopes such as plutonium and tritium. To accomplish this, the site operated five nuclear reactors and two chemical separation plants (U.S. Department of Energy, 1997). Cragle et al. conducted a mortality study of 6,687 hourly and 2,745 salaried white male production workers employed at Savannah River for at least 90 days from 1952 to 1974, with vital status follow-up through 1980. They reported non-statistically significant elevation in mortality from all leukemias combined among salaried workers (SMR = 1.05) and hourly workers (SMR = 1.63). They did report a statistically significant increase in leukemia mortality among hourly employees first hired before 1955 and employed between 5 and 15 years (SMR = 2.75; 95% CI 1.01, 5.99) (Cragle et al., 1988).

In 1998, Cragle et al. updated this mortality study by including six additional years of follow-up. Using a two-year lag period, they reported a significant trend of increased leukemia mortality with increased radiation exposure among the 20 non-CLL leukemia deaths (Chi-square 1 df = 3.86, $p < 0.05$). They also reported an elevated excess relative risk of 13.6% (90% CI 0.61, 50.62) per 10 mSv of cumulative dose for non-CLL cases (Cragle et al., 1999; Schubauer-Berigan and Wenzl, 2001). [Sievert (Sv) is the measure of dose equivalent in SI. It is the product of absorbed dose in grays and a weighting factor for radiation type. (Borders, 1991)]

7.8.3. The United States Department of Energy Oak Ridge National Laboratory (ORNL)

The Oak Ridge facility is located on 58,000 acres, approximately 20 miles west of Knoxville, Tennessee. Established in the early 1940s, its primary functions have included lithium enrichment and storage, and the production of enriched and commercial grade uranium, ceramic weapons components, and radioisotopes (U.S. Department of Energy, 1997). Wing et al. conducted a mortality study of 8,318 white men employed for at least 30 days at the Oak Ridge National Laboratory from 1943 to 1972, who were followed up for vital status through 1984. They reported a significant increase in leukemia mortality in all workers (SMR = 1.63; 95% CI

1.06, 2.35) and workers who were monitored for exposure to internal radiation (SMR = 2.23; 95% CI 1.27, 3.62) (Wing et al., 1991). Frome et al. conducted a mortality study of 28,347 white males employed for at least 30 days at either the Oak Ridge National Laboratory or the Oak Ridge Y-12 facility from 1943 to 1985, who were followed up for vital status through 1985. They reported no positive association between leukemia mortality and external ionizing radiation exposure among the workers (Frome et al., 1997). Gilbert et al. conducted a multi-site mortality study of radiation-monitored workers that included 32,643 male and female Hanford workers, 6,348 male Oak Ridge National Laboratory workers, and 5,952 male workers from the Rocky Flats Weapons Plant in Colorado. They reported no exposure related increase in leukemia mortality risk for the three sites combined (Gilbert et al., 1993).

7.8.4. The Department of Energy Los Alamos National Laboratory

The Los Alamos National Laboratory (LANL) covers 75 square miles in northern New Mexico. Established in 1943, its primary functions included the design and development of nuclear weapons and nuclear weapons components, and the production of small quantities of plutonium metal. The current focus at LANL is academic and industrial research (U.S. Department of Energy, 1997). Wiggs et al. conducted a mortality study of 15,727 white males employed at LANL from 1943 through 1977, with no restriction on employment duration, and with follow-up for vital status through 1994. They reported that leukemia mortality was not significantly elevated among the workers (SMR = 1.01; 95% CI 0.73, 1.35). Among the 8,318 workers who were monitored for external ionizing radiation exposure, they reported a nonsignificant positive trend between increasing exposure and lymphocytic leukemia mortality but not myeloid leukemia mortality (Wiggs et al., 1994).

7.8.5. The Mallinckrodt Chemical Works

The Mallinckrodt Chemical Works was located in St. Louis, Missouri, and processed uranium that was used as a fuel for the first nuclear reactors and in the first atomic bomb that was dropped on Hiroshima. In 1957, the St. Louis plant was closed and moved to Weldon Springs, Missouri, where production continued until the plant was closed in 1966 (U.S. Department of Energy, 1997). Dupree-Ellis et al. conducted a mortality study of 2,514 radiation-monitored white males employed at the Mallinckrodt facility for at least 30 days from 1942 to 1966, who were followed for vital status through 1993. They reported a nonstatistically significant elevation in leukemia mortality (SMR = 1.11; 95% CI 0.57, 1.89) (Dupree-Ellis, et al., 2000; Schubauer-Berigan and Wenzl, 2001).

7.8.6. British Nuclear Worker Studies—The Sellafield Plant

The Sellafield plant, owned by British Nuclear Fuels, began operation in 1947 for the production of plutonium for nuclear weapons (Omar, 1999). Smith and Douglas conducted an initial mortality study of 14,327 workers employed at the facility from 1947 to 1975, and followed them for vital status through the end of 1983. They reported no leukemia excess among the workers (Smith and Douglas, 1986). However, in a follow-up study by Douglas et al. that

extended vital status follow-up through 1988, a significant positive association between cumulative external radiation exposure and leukemia mortality (two-year lag; $p = 0.009$) was reported among the 10,276 radiation workers. The average cumulative exposure of the radiation workers was 128.1 mSv (Douglas et al., 1994). Omar et al. updated the study by adding a year of follow-up to the cohort; they also reported a significant positive association between cumulative external radiation exposure and leukemia mortality (no lag; $p = 0.03$; two-year lag; $p = 0.05$) (Omar, 1999).

7.8.7. *The United Kingdom's National Registry for Radiation Workers (NRRW)*

Established in 1976, this national registry currently includes approximately 125,000 British men and women who have been exposed to ionizing radiation and for whom exposure records were kept. Nuclear workers included in the registry were employed at nuclear weapons production facilities, defense facilities, nuclear medicine production companies, and nuclear utility companies (Muirhead et al., 1999; Schubauer-Berigan and Wenzl, 2001). Kendall et al. conducted a mortality study that included 95,217 radiation workers employed by five major British nuclear industry facilities who participated in the NRRW. They reported a significant positive association between cumulative external radiation exposure and non-CLL leukemia mortality ($p = 0.03$) (Kendall et al., 1992). The excess leukemia risk however, was evident at only one of the five facilities (Sellafield) included in the study (Boice and Inskip, 1996). Muirhead et al. conducted a second NRRW study which included an expanded cohort of 124,743 workers, with vital status follow-up extended through the end of 1992 for all workers. They reported borderline evidence of a positive association between cumulative external radiation exposure and non-CLL leukemia mortality ($p = 0.067$) (Muirhead et al., 1999).

7.8.8. *Russian Nuclear Workers— The Mayac Production Complex*

The Mayac production complex was the first nuclear complex built in the former Soviet Union. The complex, located in the Southern Ural Mountains, began operation in 1948 and included a nuclear reactor, a radiochemical plant for the chemical separation of plutonium from irradiated nuclear fuel, and a plutonium production plant (Koshurnikova, 1999). It has been reported that there were several technological failures during the early years of operation that resulted in large releases of radionuclides, exposing workers and local populations (Kossenko et al., 2000). It has also been reported that 6.5% of the nuclear reactor workers and 22.8% of workers employed in the radiochemical plant working from 1948 to 1953 received annual doses equal to or greater than 1Gy (Schubauer-Berigan and Wenzl, 2001). Koshurnikova et al. conducted a mortality study of 8,855 Mayak workers employed from 1948 through 1972. They reported no excess leukemia mortality risk among reactor workers or plutonium production workers. They did report a statistically significant excess in leukemia mortality among the 1,839 males who worked in the radiochemical processing facility (SMR= 3.17; 95% CI 1.45, 6.93) (Koshurnikova, et al., 1996). A major limitation of the Mayac worker mortality studies is lack of a well developed national disease rate tracking system in the former Soviet Union (Schubauer-Berigan and Wenzl, 2001).

7.8.9. *The Chernobyl Clean-Up Workers*

The Chernobyl Nuclear Power Plant accident occurred on April 26, 1986, and resulted in large-scale fires, explosions, and both immediate and delayed deaths of plant operators and emergency service workers called to the site. Large amounts of radioactive nuclides that included krypton, xenon, cesium, iodine, strontium, and plutonium were released, contaminating a large land area surrounding the plant (Ginzburg and Reis, 1991). Following the accident, 600,000 workers were sent to the site to clean up the environment and entomb the reactor. Typical occupational exposures for the workers were stated to be 0.35 Gy. [Gray (Gy) is the name of the SI unit of absorbed dose. $1 \text{ Gy} = 1 \text{ J Kg}^{-1} = 100 \text{ rad}$ (Boice and Inskip, 1996)]. To date there have been no significant additional cancers reported among the clean-up workers (Goldman, 1997). Rahu et al. conducted a mortality study of 4,742 men from Estonia who had participated in the Chernobyl cleanup from 1986 to 1991. They reported a total of 144 deaths were observed (SMR = 0.98; 95% CI 0.82, 1.14) and no increased incidence of either all cancers (25 incident cases observed vs. 26.5 expected) or leukemia (no cases observed vs. 1.0 expected) (Rahu et al., 1997).

7.9. *Exposures from Medical X-Ray Treatment*

7.9.1. *Ankylosing Spondylitis*

There have been several mortality studies of British patients diagnosed with ankylosing spondylitis who received x-ray therapy as a treatment (Brown and Doll, 1965; Radford et al., 1977; Smith et al., 1982). Ankylosing spondylitis is a progressive rheumatic disease that mainly affects the spine and is characterized by the fusion of joints and bones (Taylor, 1988). Darby et al. conducted a mortality study that included 14,106 British patients with ankylosing spondylitis who had been given a single course of x-ray treatment during 1935 and 1954. They reported a three-fold increase in leukemia mortality, and that mortality risk was highest from 2.5 to 4.9 years after the treatment (Darby et al., 1987). Weiss et al. conducted a mortality study of 15,577 adult ankylosing spondylitis patients, of whom 14,556 had received radiation treatment typically given once a day for a two-week period. The vital status of the patients was followed through 1991. They reported that among the patients receiving radiation therapy there was a significant increase in leukemia mortality (RR = 2.74, 95% CI 2.10, 3.53) (Weiss et al., 1994).

7.9.2. *Cervical and Uterine Cancer Treatment*

Radiation therapy for the treatment of cervical and uterine cancers involves extensive exposure of the active bone marrow to ionizing radiation and has been linked in some studies to the development of secondary leukemia. Boice et al. examined the frequency of occurrence and type of second cancers among 182,040 women treated for cervical cancer. They reported that among the 82,616 women who were treated with fractionated doses of radiation from 1935 to 1970, there was a 1.3-fold excess of acute and non-lymphocytic leukemia (Boice et al., 1985). Curtis et al. examined 110,000 women who were diagnosed with invasive uterine cancer from 1935 through 1985 and received partial-body radiation therapy. They reported that radiotherapy did not increase the risk of CLL (RR = 0.90; 95% CI 0.4, 1.9). However, for all leukemias combined

excluding CLL, they reported a significant risk of leukemia (RR = 1.92; 95% CI 1.3, 2.9) (Curtis et al., 1994).

7.9.3. Breast Cancer

Excess incidence of AML has been reported in studies of breast cancer patients treated with radiation therapy during oncology clinical trials (Fisher et al., 1985; Linet and Cartwright, 1996). Andersson et al. conducted a study of the incidence of new primary cancers among 3,538 postmenopausal Danish patients who had received surgical treatment for primary breast cancer. They reported an increased incidence of AML among the patients who received postoperative radiotherapy (Andersson et al., 1991; Linet and Cartwright, 1996). Curtis et al. conducted a nested case-control study that included 48 women diagnosed with breast cancer from 1935 to 1972 who received radiation therapy and later developed leukemia. They reported that radiation therapy did not increase the overall risk of leukemia (RR = 1.16; 90% CI, 0.6, 2.1) (Curtis et al., 1989). Curtis et al. conducted another case-control study in 1992 that included 90 women diagnosed with breast cancer from 1973 to 1985 who received radiation therapy and were later diagnosed with leukemia. They reported that the risk of leukemia was significantly increased for women who received radiation therapy only without alkylating agents (Curtis et al., 1992).

8. Occupations Associated with Increased Risk of Leukemia

8.1. Radiologists and X-Ray Technicians

Smith and Doll conducted a mortality study of males who joined the British Radiological Society from 1897 to 1954. They reported that radiologists who entered the profession prior to 1921 suffered a six-fold increase in leukemia mortality risk, while individuals who entered the profession after 1921 had no increase in leukemia mortality risk (Smith and Doll, 1981; Linet and Cartwright, 1996). Matanoski et al. conducted a mortality study of U.S. radiologists who joined the Radiological Society of North America over a 50-year period beginning in 1920. They reported that radiologists who joined the society from 1920 to 1929 had an 8.8-fold increase in leukemia mortality and radiologists who joined between 1930 and 1939 had a 3.4-fold increase in leukemia mortality. They reported no excess leukemia mortality among radiologists who joined the society after 1940 (Matanoski et al., 1975; Linet and Cartwright, 1996). Other mortality studies of U.S. radiologists (Logue et al., 1986) and radiologic technologists (Doody et al., 1998) have reported no increase in leukemia mortality among workers employed after 1940 (Schubauer-Berigan and Wenzl, 2001).

8.2. Garage and Transportation Maintenance Workers

Some studies have reported a possible increase in leukemia mortality risk among highway transportation maintenance workers (Linet and Cartwright, 1996). The Minnesota Department of Health conducted a cohort mortality study of 4,849 workers employed by the Minnesota Highway Maintenance Department from 1945 to 1984. Leukemia mortality was significantly elevated (SMR = 4.25; 95% CI 1.71, 8.76) among workers employed 30 to 39 years (Bender,

1989). The American Cancer Society conducted a prospective mortality study of 461,981 males ages 40 to 79 who were exposed to diesel exhaust and reported an association based on small numbers with increased leukemia mortality (Boffetta et al., 1988). It is thought that a possible increased risk of leukemia among maintenance workers reported in these studies could be due to a variety of exposures such as diesel fuels, asphalts and tars, herbicides, gasoline, aromatic hydrocarbons, and benzene (Linnet and Cartwright, 1996).

8.3. Painters

Painters are exposed to various complex mixtures, including dyes, pigments, and organic solvents with known carcinogenic potential (Bethwaite et al., 1990). In 1989, the International Agency for Research on Cancer (IARC) determined that there was sufficient evidence that certain cancers could result from occupational exposures as a painter (IARC, 1989). Matanoski et al. conducted a cohort mortality study of 57,175 members of the International Brotherhood of Painters and Allied Trades (IBPAT) who were employed in the United States from 1975 through 1979. Members of the cohort were categorized into mixed local unions that were composed primarily or exclusively of painters and specialty local unions that included members of specific allied trades such as glaziers, tile and carpet layers, and wood finishers. The mortality experience of members of the mixed local unions was compared to that of the specialty local unions and a statistically significant difference in leukemia mortality was reported (SMR = 1.23 for the mixed group; SMR = .51 for the specialty group; $p = 0.022$) (Matanoski et al., 1986). A case-control study that included 125 Swedish adults diagnosed with acute leukemia and 125 matched controls reported that regular exposure to solvents is associated with an increase risk of developing acute leukemia. The study also reported that painters whose median time of solvent exposure was 16 years had the greatest increased risk (OR = 13; 95% CI 2.0, 5.54) of acute leukemia (Lindquist, 1987). Bethwaite et al. conducted a series of case-control studies whose cases and controls were selected from a group of 19,904 individuals over the age of 20 and listed on the New Zealand cancer registry from 1980 to 1984. The goal of the study was to examine a possible association between cancer mortality from different types of cancer (including leukemia) and work as a painter. The study reported no increased risk of leukemia mortality (OR = 0.54; 95% CI 0.23, 1.30) among painters (Bethwaite et al., 1990). It is thought that a variation in the composition of the paint used in Sweden and New Zealand may possibly account for the different findings reported by Lindquist and Bethwaite (Linnet and Cartwright, 1996). A meta-analysis conducted by Chen and Seaton in 1998 reported excess leukemia risk among painters (SMR = 187; 95% CI 114.5, 306.7). The excess deaths from leukemia however, could have been due to exposure to benzene mixed with other organic solvents (Chen and Seaton, 1998).

8.4. Welders

Welders are exposed to a variety of airborne contaminants, depending upon the specific technology and materials used in the welding process. Some epidemiological studies have reported elevated leukemia risk among welders (Linnet and Cartwright, 1996). In a review of eleven epidemiologic surveys that examined leukemia and occupational exposure to

electromagnetic fields, Savitz and Calle reported no elevated risk among welders from all leukemias (RR = 0.9; 95% CI 0.7, 1.2), or acute leukemia (RR = 1.0; 95% CI 0.7, 1.5) and a nonstatistically significant elevation in acute myelogenous leukemia (RR = 1.7; 95% CI 0.5, 4.5) (Savitz and Calle, 1987). A case-control study of 130 CML patients in Los Angeles County, California, reported a significant association between occupation as a welder and CML (Crude OR = 19; 95% CI 2.78, 232.54) (Preston-Martin and Peters, 1988). A nested case-control study within a population of 24,545 male nuclear shipyard workers in Portsmouth, New Hampshire reported an elevated risk of all leukemia (OR = 2.3; 95% CI 0.92, 5.5) and a statistically significant increased risk of myeloid leukemia (OR = 3.8; 95% CI 1.3, 11.5) among welders (Stern et al., 1986). Because there is limited evidence in humans and inadequate evidence in experimental animals for the carcinogenicity of welding fumes and gases, the International Agency for Research on Cancer (IARC) has concluded that welding fumes are only possibly carcinogenic to humans (IARC, 1990).

8.5. Electrical Workers

Epidemiological studies have inconsistently reported a positive association between electromagnetic field exposure and leukemia among electrical workers (Villeneuve et al., 2000). Coleman and Beral conducted a review of eleven studies conducted from 1978 to 1988 that examined the health effects of exposure to extremely low frequency (ELF) non-ionizing electromagnetic fields. They performed a pooled analysis of these studies and reported an excess risk of leukemia (RR = 1.18; 95% CI 1.09, 1.29) and acute myeloid leukemia (RR = 1.46; 95% CI 1.27, 1.65) among electrical workers (Coleman and Beral, 1988). It was not possible to determine from these studies if the elevated leukemia was due to electromagnetic fields or other exposures such as benzene, or if the increase is specific to certain jobs within the electrical industry (Shore, 1988 and Theriault, 1992). A New Zealand case-control study of 110 incident leukemia cases diagnosed between 1989 and 1991 reported an elevated risk of acute leukemia among electrical workers (OR = 1.9; 95% CI 1.0, 3.8). An exposure-response effect was also reported with acute leukemia rising with increasing occupational magnetic field exposure (Bethwaite et al., 2001). In 1989, a series of case-control studies were conducted involving 19,904 male cancer patients over the age of twenty and diagnosed from 1980 to 1984 from the New Zealand Cancer Registry. An elevation in leukemia risk among electrical workers (OR = 1.62; 95% CI 1.04, 2.52) was reported, which was primarily due to chronic leukemia (OR = 2.12), not acute leukemia (Pearce et al., 1989). A study of active-duty naval personnel from 1974 to 1984 reported a small elevated incidence of leukemia among individuals employed as electrician's mate (SIR = 2.4; 95% CI 1.0, 5.0) (Garland, 1990). Other studies of electrical workers have reported no excess risk of leukemia. A nested case-control study of Norwegian railway workers, however, reported no elevation in leukemia mortality among men employed on electric railways compared with those employed on non-electric railways (Tynes et al., 1994). A cohort study of 138,905 men employed at five electric power companies in the United States from 1950 to 1986 did not support an association between leukemia and occupational magnetic field exposure (Savitz and Loomis, 1995). Also, a case-cohort analysis of male electric utility

workers who died of leukemia selected from this cohort of 138,905 reported no association between leukemia and electromagnetic field exposure (Savitz et al., 2000).

Appendix B – Tables

Table 1: Cancer Mortality in the United States (Males) 1950-1991

Cancer Mortality in the United States Changing Patterns for 11 Major Cancers in U.S. Males, 1950-1991

Death Rates for Males, per 100,000, for 11 Sites
1950-1991, Age-adjusted to 1970 U.S. Standard Population

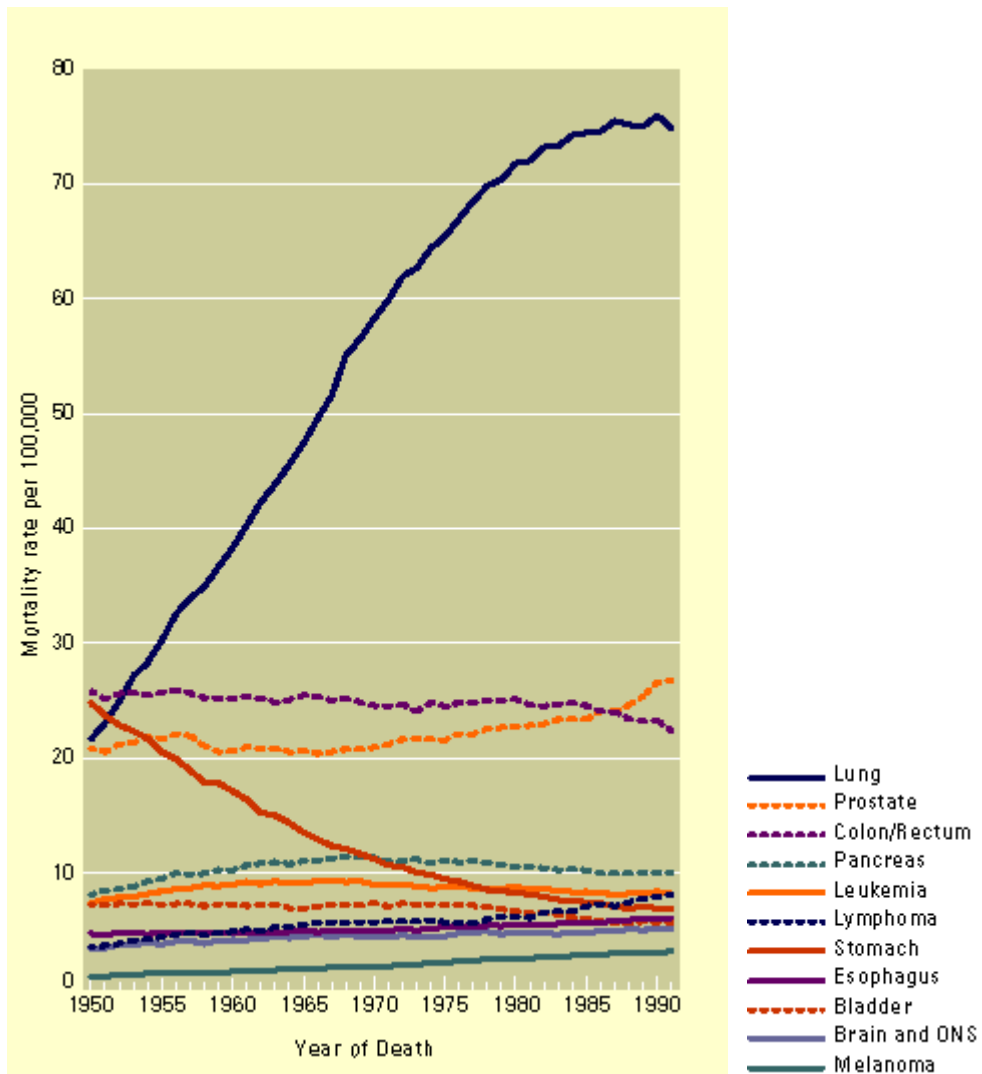


Table 2: Cancer Mortality in the United States (Females) 1950-1991

**Cancer Morality in the United States
Changing Patterns for 12 Major Cancers in U.S. Females, 1950-1991**

**Death Rates for Females, per 100,000, for 12 Sites,
1950-1991, Age-adjusted to 1970 U.S. Standard Population**

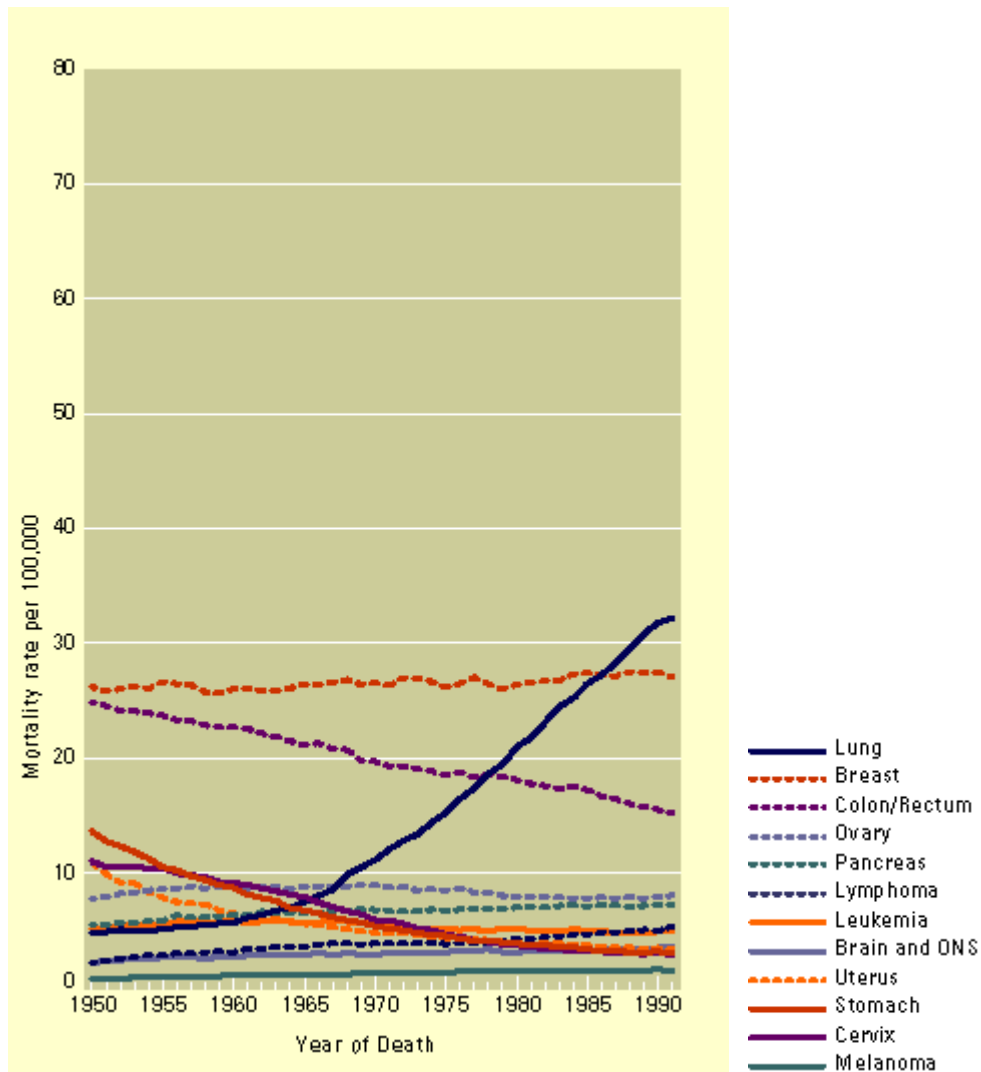


Table 3: Mortality—All Leukemia Types Combined—Males

**All Leukemia Types Combined—Males
U.S. Mortality Age-Adjusted Rates—1973-1999**

**Standard Population = 2000 U.S.
Age at death = All Ages
(Rates are from the NCHS public use data file)**

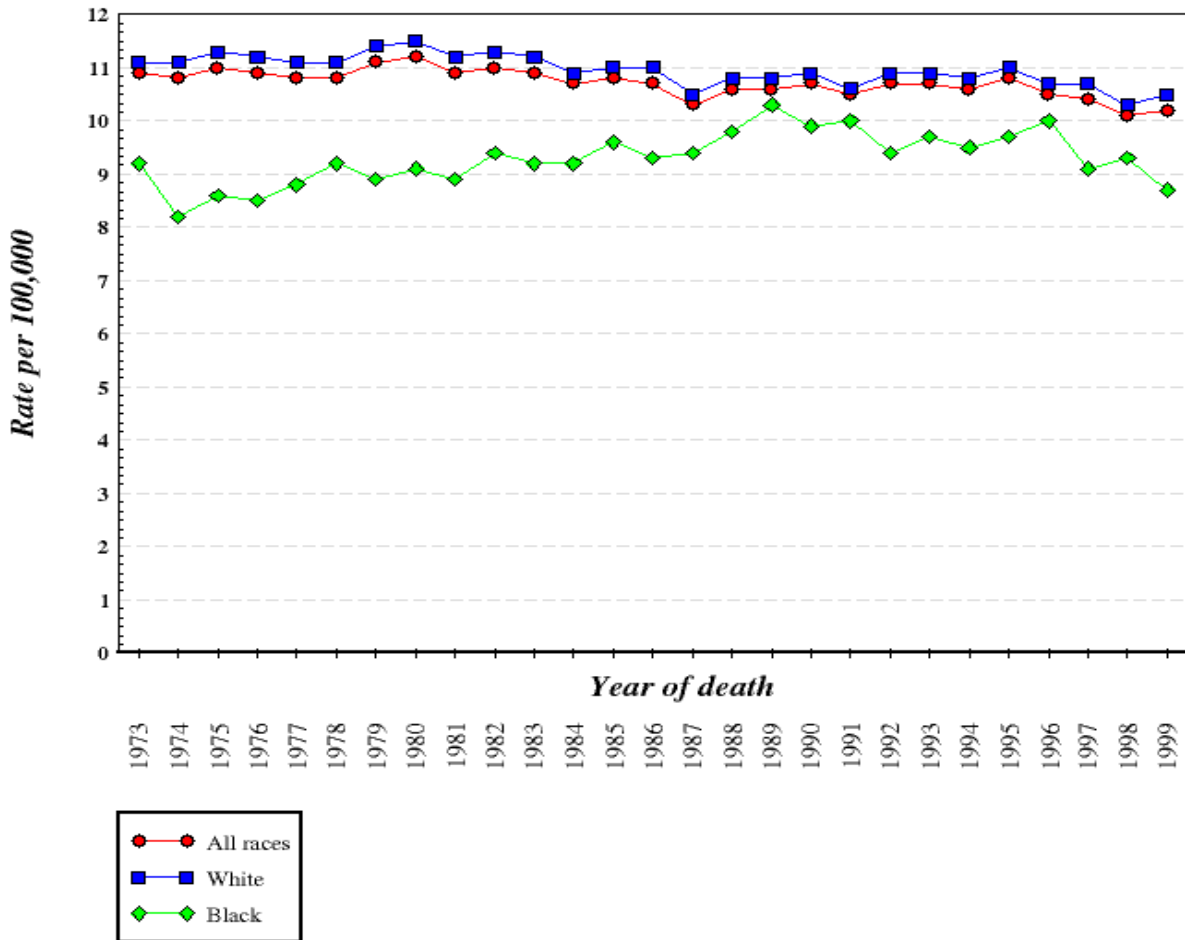


Table 4: Mortality—All Leukemia Types Combined—Females

**All Leukemia Types Combined—Females
U.S. Mortality Age-Adjusted Rates—1973-1999**

**Standard Population = 2000 U.S.
Age at Death = All Ages
(Rates are from the NCHS public use data file)**

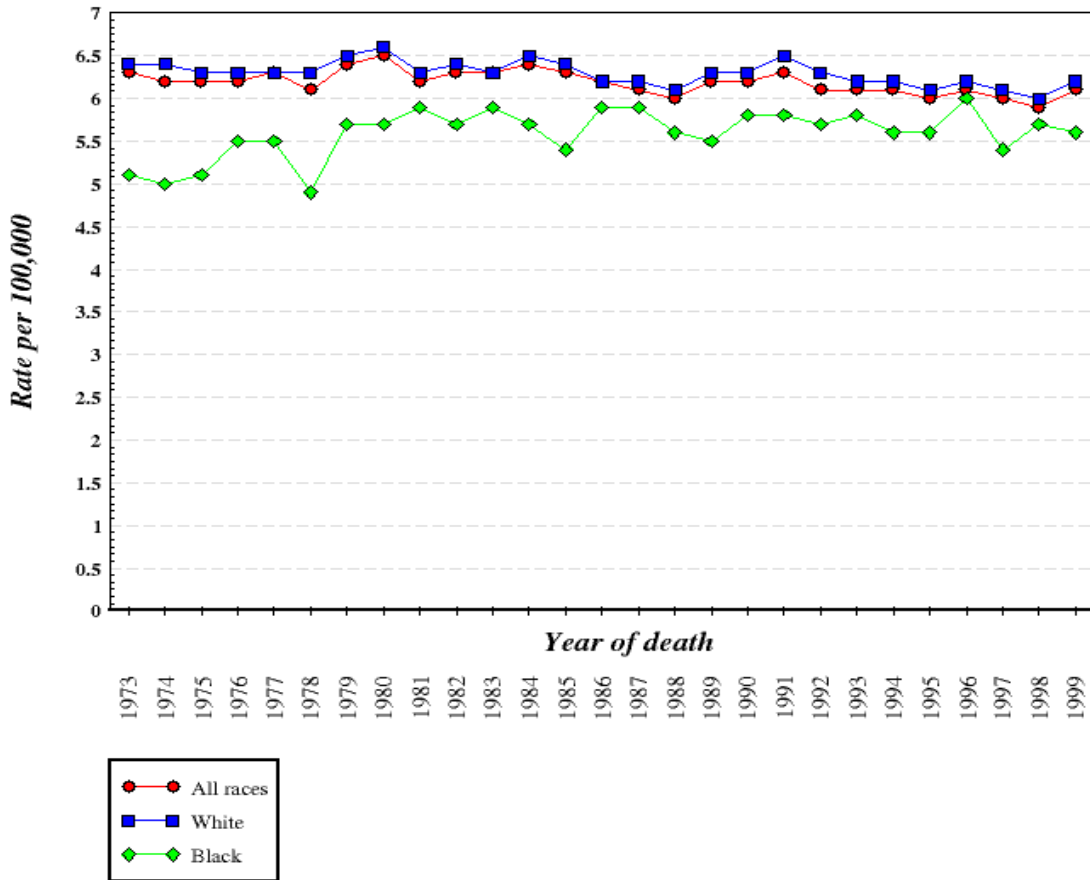


Table 5: SEER Incidence and Mortality Rates—1973—1999

**SEER Incidence and Mortality Rates for All Leukemia Types Combined:
White and Black Males and Females
1973—1999 (Reis et al., 2002)**

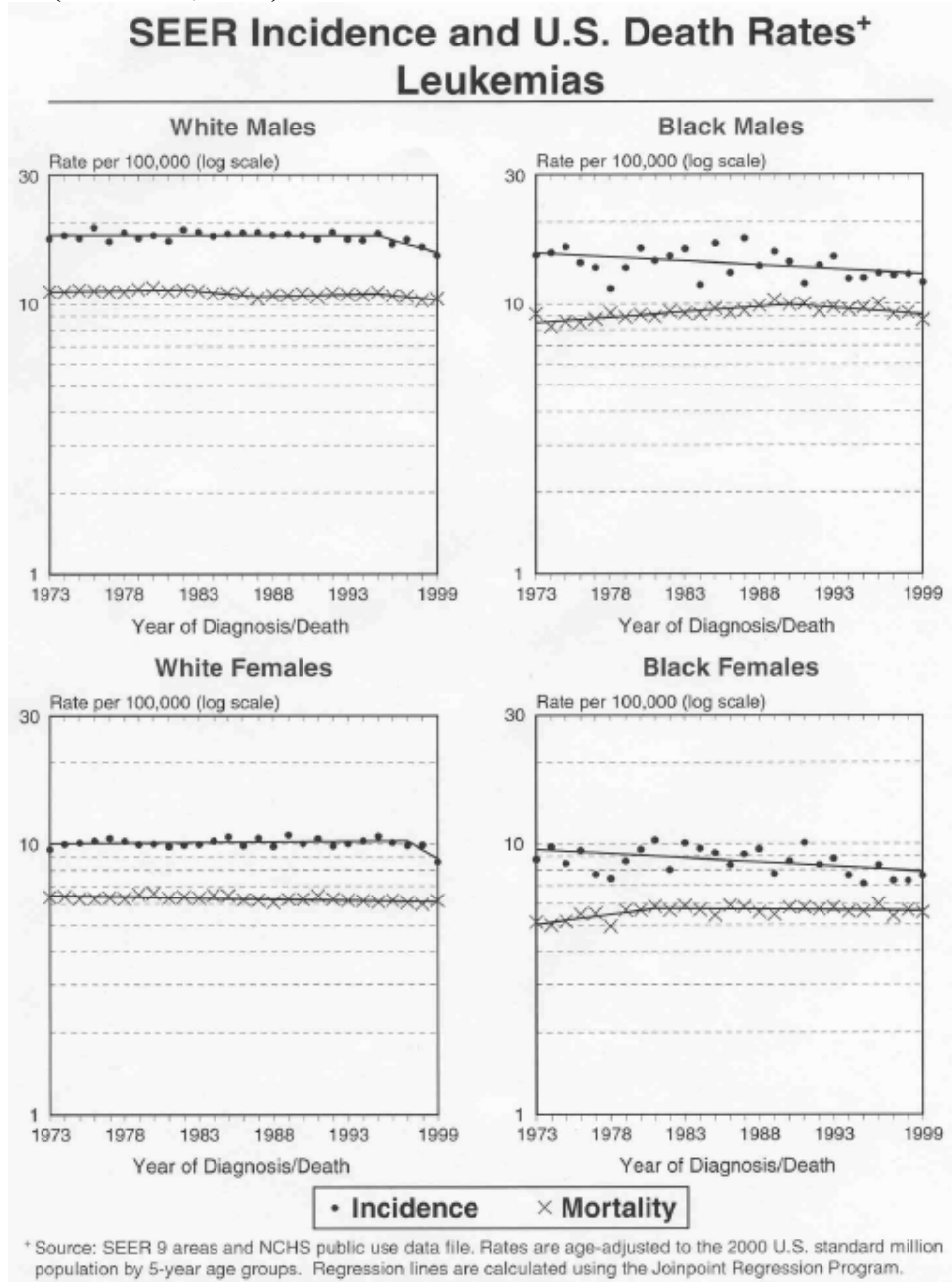


Table 6: Acute Myeloid Leukemia—Incidence—1973-1999

Acute Myeloid Leukemia—Incidence
SEER Incidence Age-Adjusted Rates
Standard population = 2000 U.S.
Year of diagnosis = 1973-1999

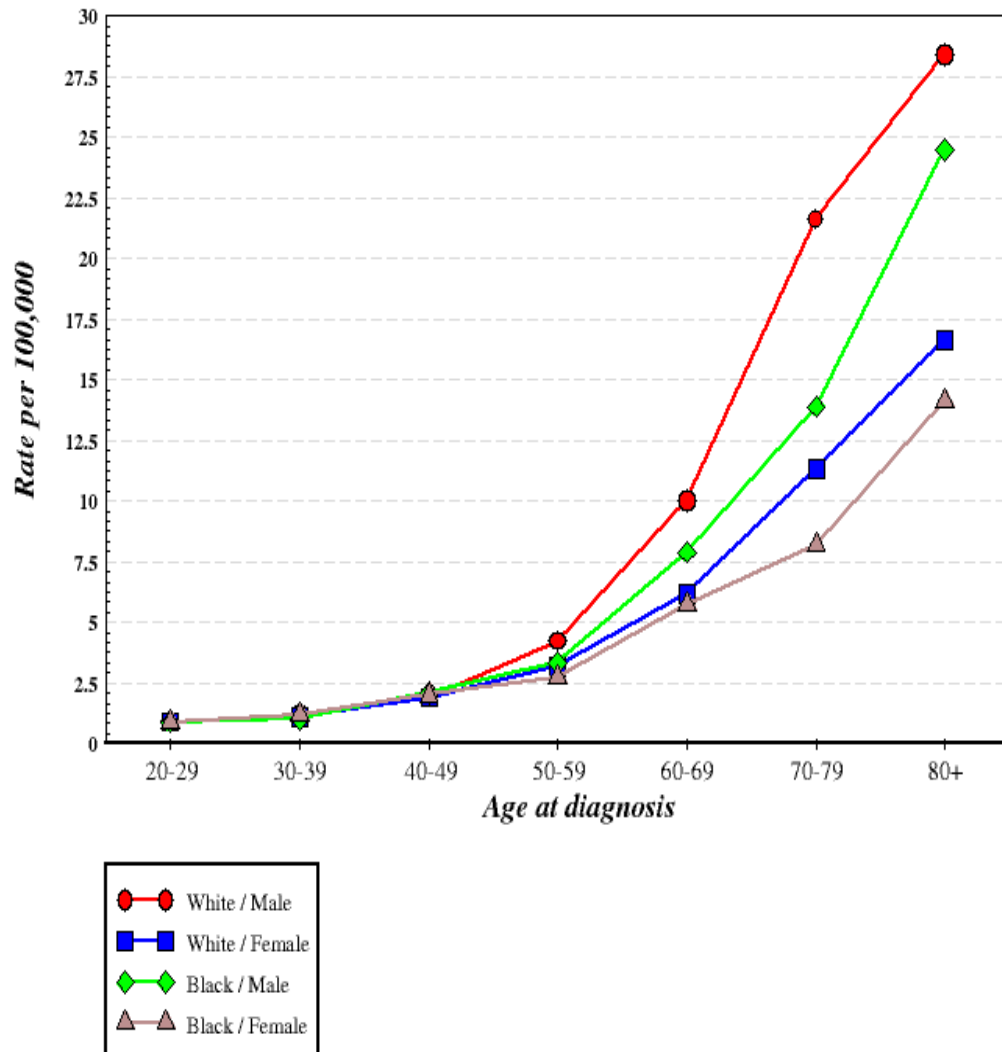


Table 7: Acute Myeloid Leukemia—Mortality—1969-1999

Acute Myeloid Leukemia—Mortality
SEER Mortality Age-Adjusted Rates
Standard population = U.S. 2000
Year of death = 1969-1999

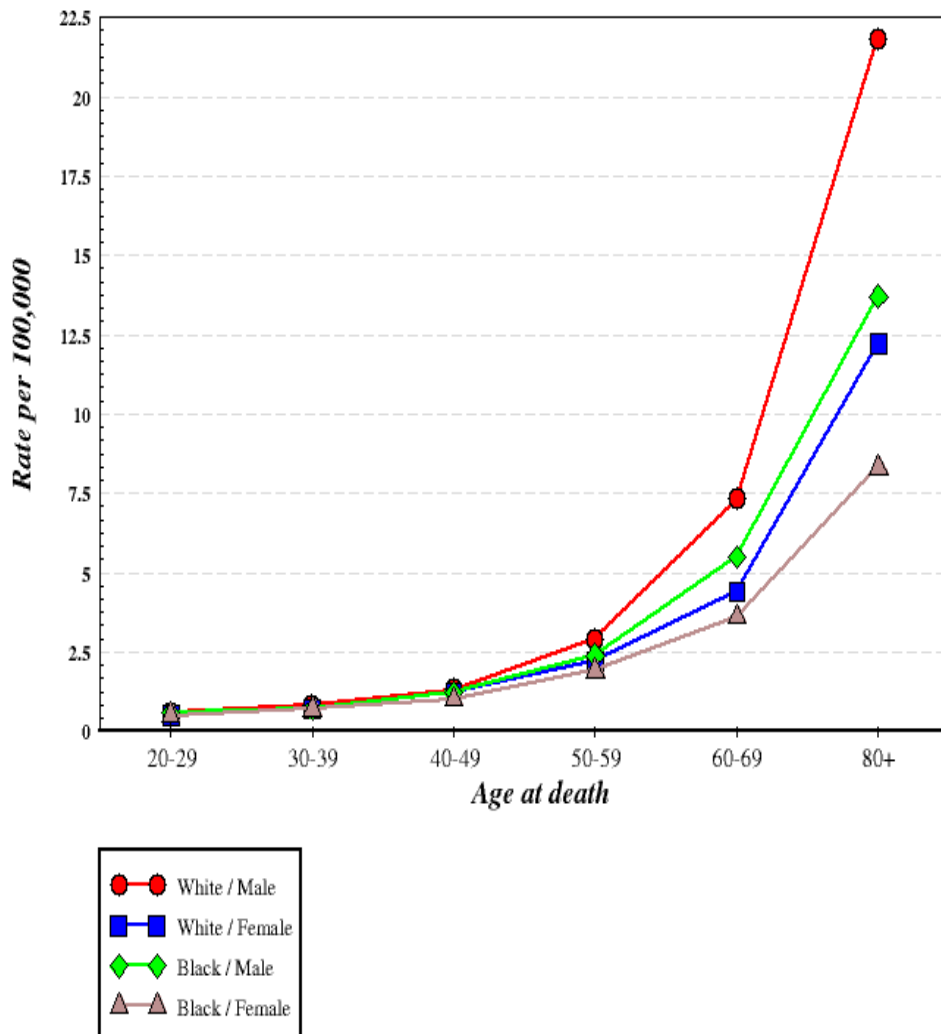


Table 8: Chronic Lymphocytic Leukemia—Incidence—1973-1999

Chronic Lymphocytic Leukemia—Incidence
SEER Incidence Age-Adjusted Rates
Standard population = 2000 U.S.
Year of Diagnosis = 1973-1999

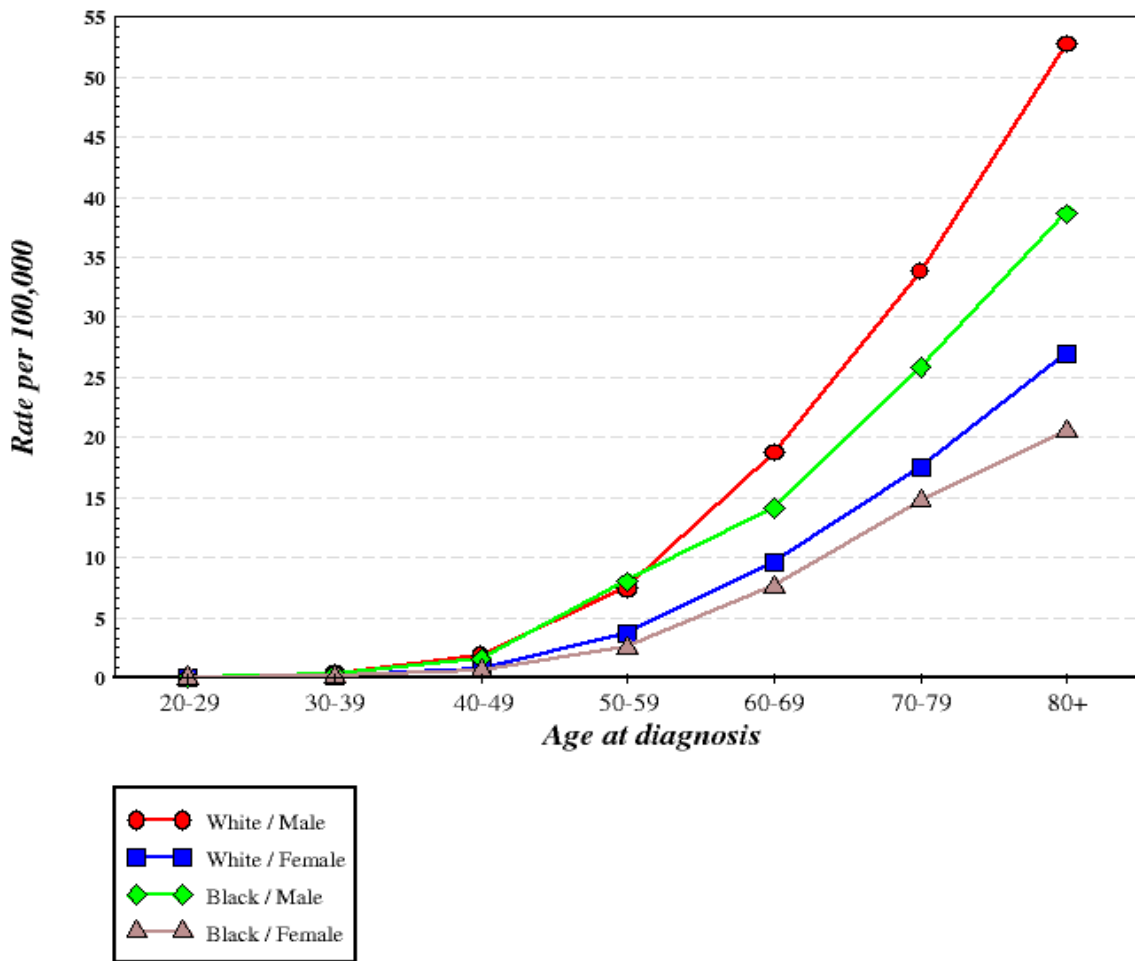


Table 9: Chronic Lymphocytic Leukemia—Mortality—1969-1999

Chronic Lymphocytic Leukemia—Mortality
SEER Mortality Age-Adjusted Rates
Standard population = 2000 U.S.
Year of death = 1969-1999

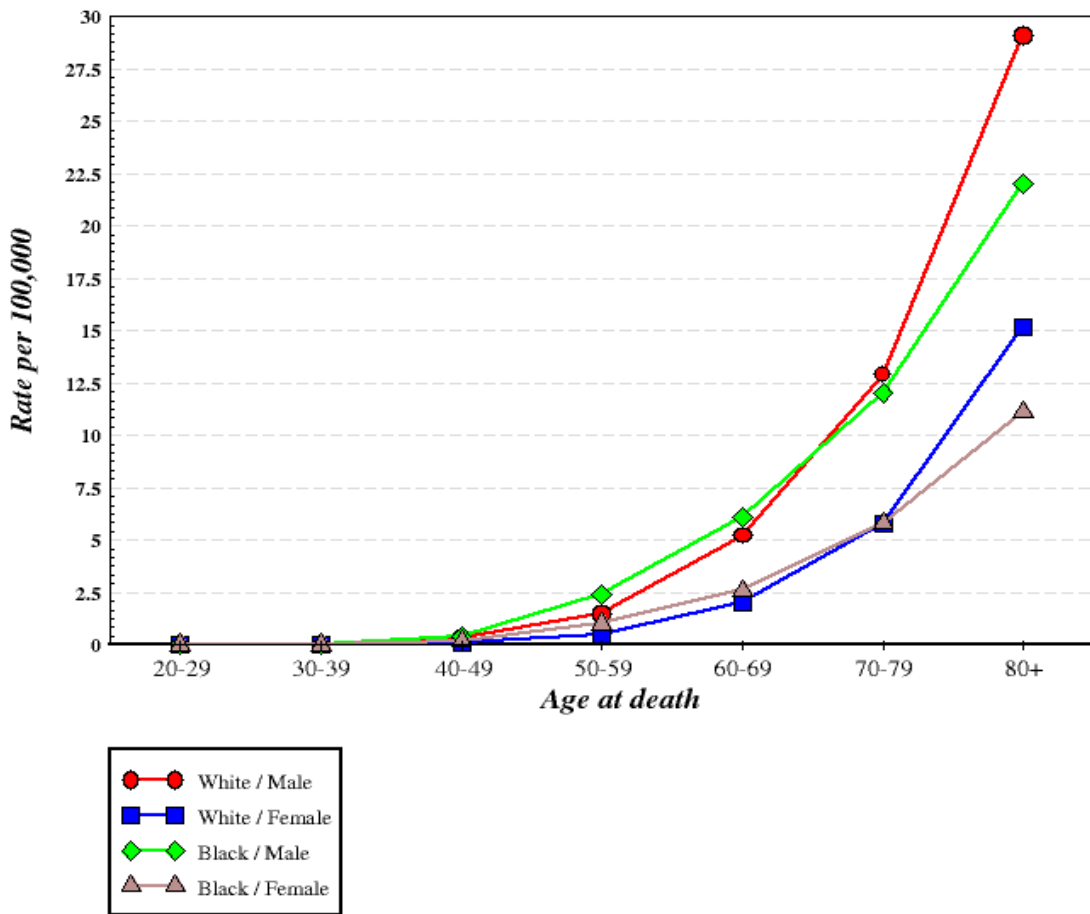


Table 10: Chronic Myeloid Leukemia—Incidence—1973-1999

Chronic Myeloid Leukemia—Incidence
SEER Incidence Age-Adjusted Rates
Standard population = 2000 U.S.
Year of diagnosis = 1973-1999

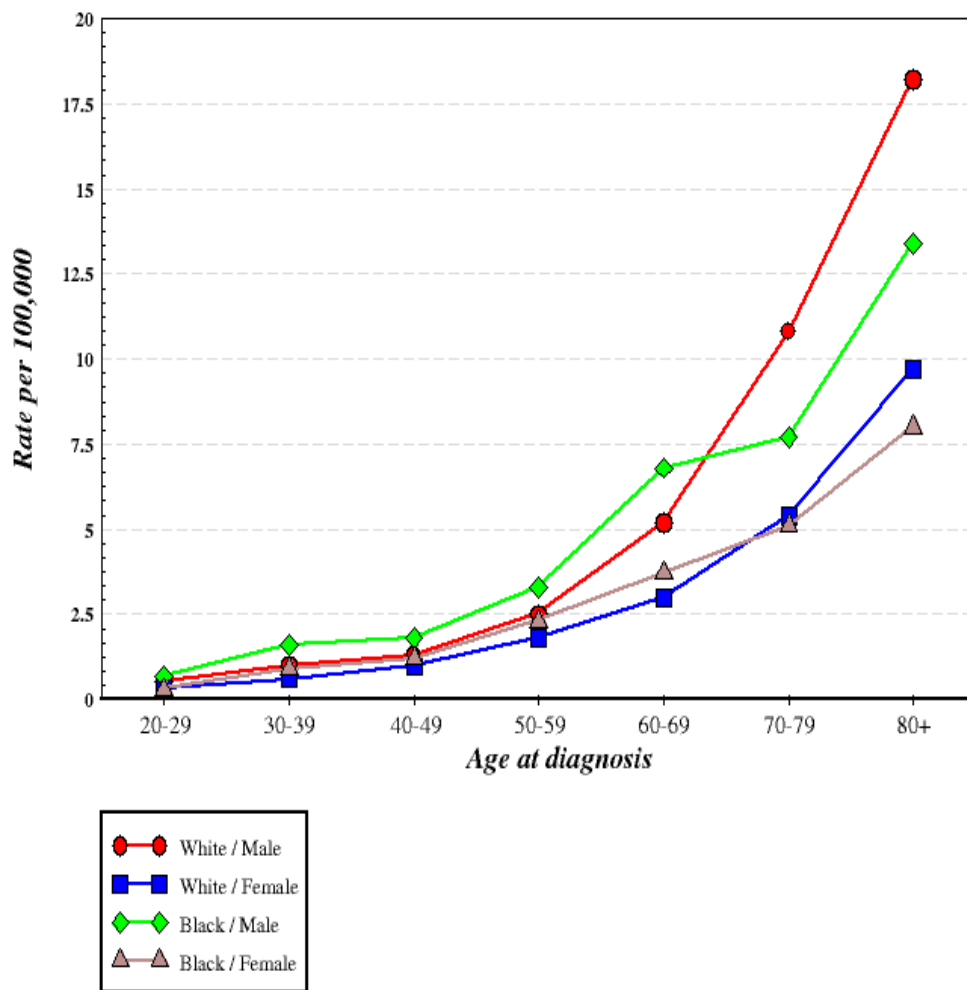


Table 11: Chronic Myeloid Leukemia—Mortality—1969-1999

Chronic Myeloid Leukemia—Mortality
SEER Mortality Age-Adjusted Rates
Standard population = 2000 U.S.
Year of Death = 1969-1999

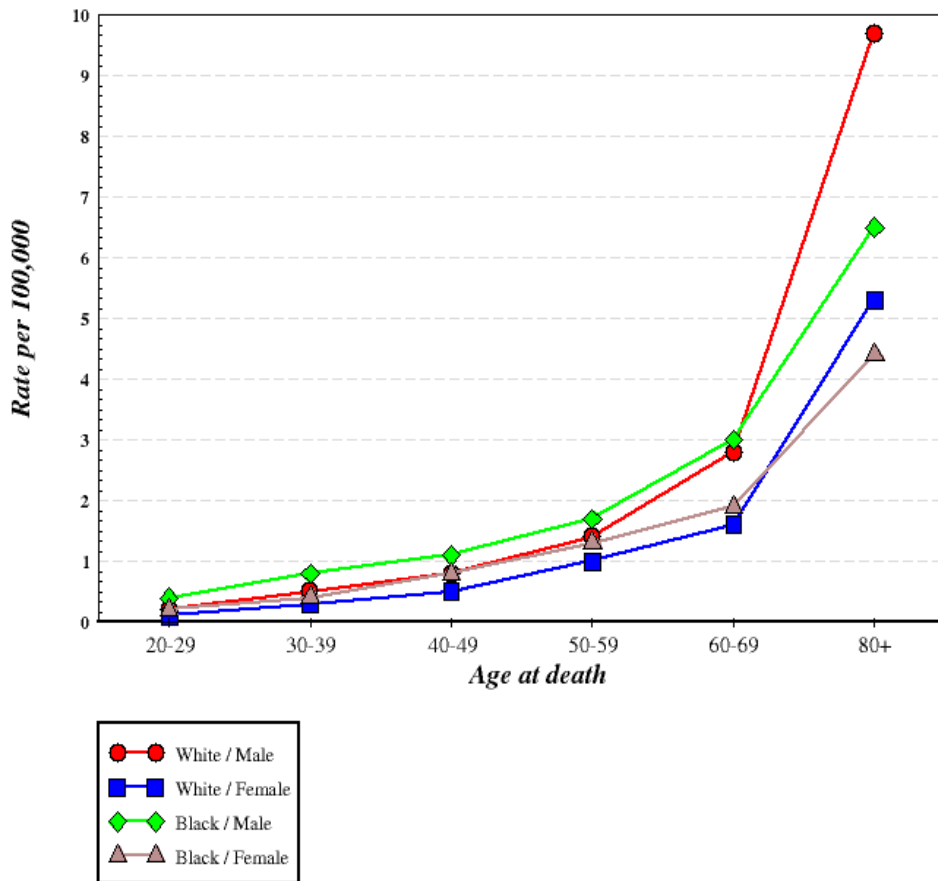


Table 12: Acute Lymphocytic Leukemia—Incidence—1973-1999

Acute Lymphocytic Leukemia—Incidence
SEER Incidence Age-Adjusted Rates
Standard population = 2000 U.S.
Year of diagnosis = 1973-1999

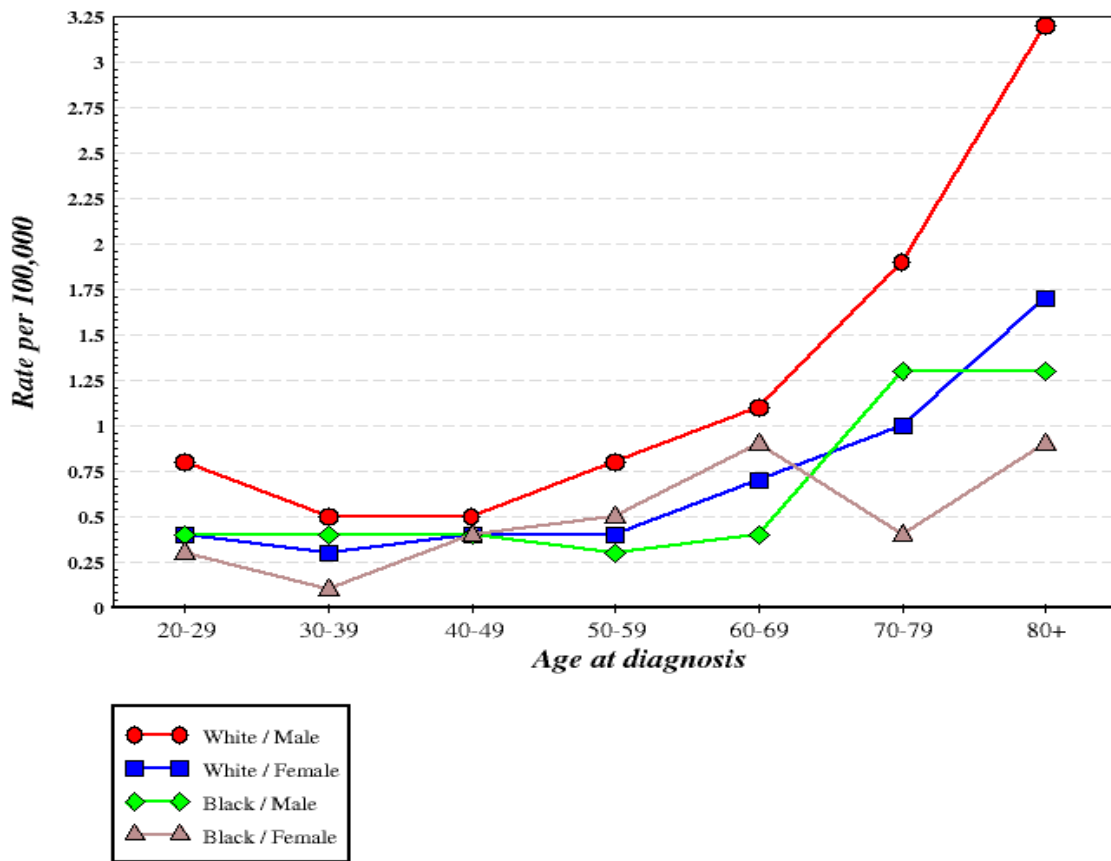
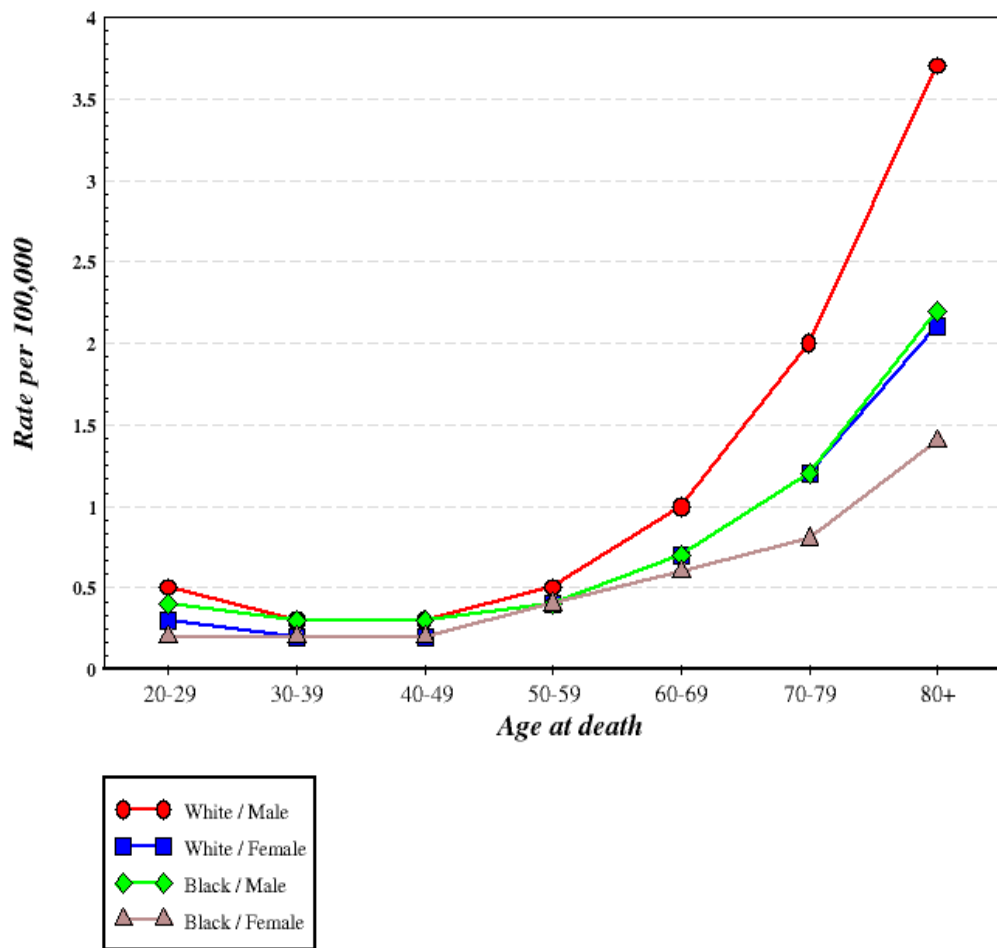


Table 13: Acute Lymphocytic Leukemia—Mortality—1969-1999

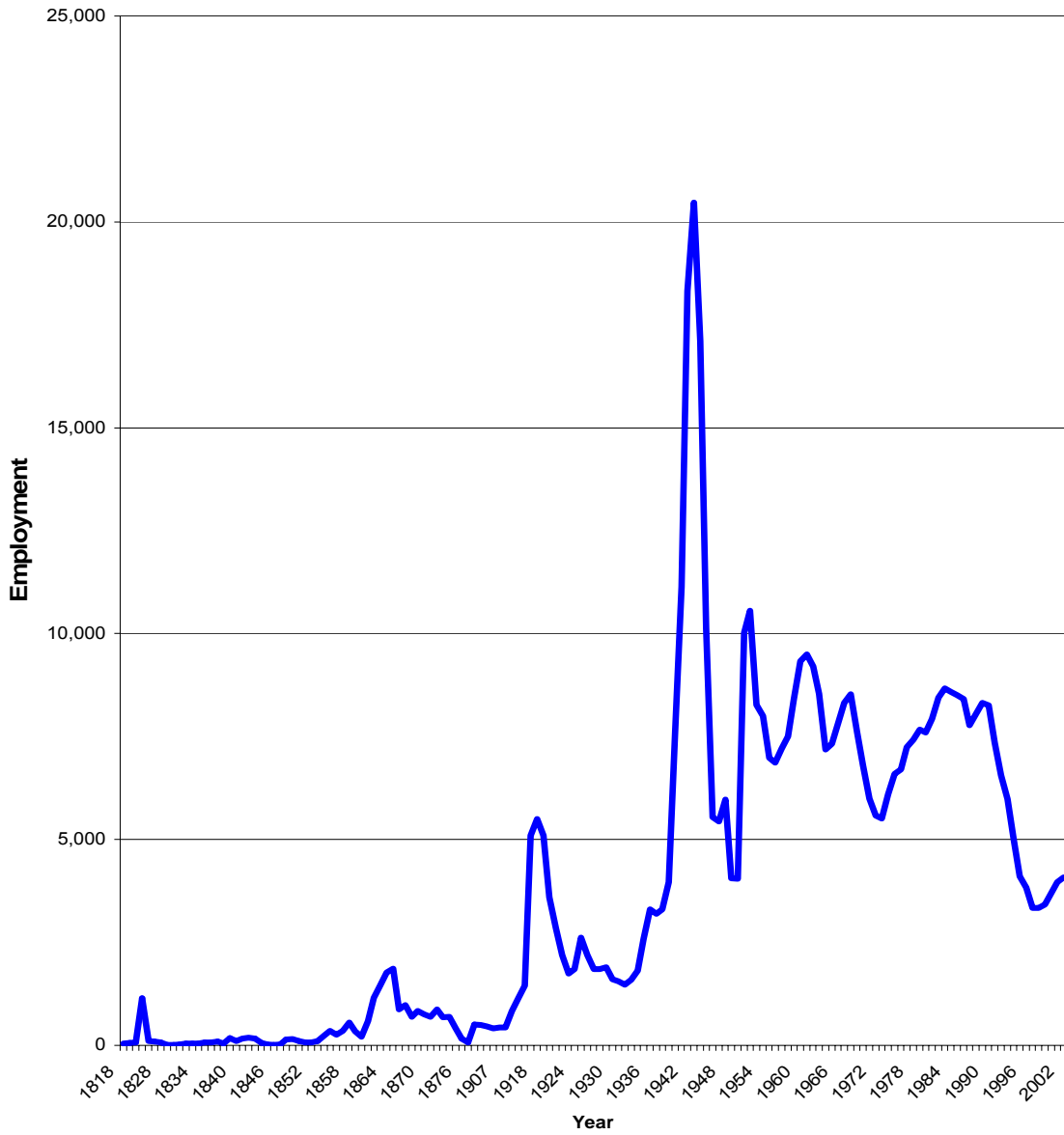
Table 13: Acute Lymphocytic Leukemia—Mortality
SEER Mortality Age-Adjusted Rates
Standard population = 2000 U.S.
Year of death = 1969-1999



Appendix C

Number of Civilian Employees Working at the PNS by Fiscal Year

**Portsmouth Naval Shipyard Employment
By Fiscal Year**



Appendix D

List of Construction, Overhauls, and Scheduled Maintenance October 1, 1955, to December 11, 2002

Listing of all New Nuclear Submarine Construction, Overhauls, and Scheduled Maintenance Performed by Civilian Employees at the Portsmouth Naval Shipyard

October 1, 1955—December 11, 2002

Portsmouth Naval Shipyard History Of Nuclear Submarines

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS SWORDFISH	SSN 579	New Construction	10/01/55	09/15/58
USS THRESHER	SSN 593	New Construction	04/04/58	08/01/61
USS ABRAHAM LINCOLN	SSBN 602	New Construction	08/01/58	03/08/61
USS SEA DRAGON	SSN 584	New Construction	04/01/59	12/01/59
USS NAUTILUS	SSN 571	Refueling Overhaul	06/03/59	08/10/60
USS TINOSA	SSN 606	New Construction	08/03/59	11/28/64
USS JACK	SSN 605	New Construction	04/01/60	04/21/67
USS JOHN ADAMS	SSBN 620	New Construction	02/06/61	05/16/64
USS NATHANIEL GREENE	SSBN 636	New Construction	02/01/62	12/23/64
USS SKIPJACK	SSN 585	Regular Overhaul	02/09/62	09/19/62
USS THRESHER	SSN 593	Post Shakedown Availability	07/12/62	04/10/63
USS GRAYLING	SSN 646	New Construction	03/04/63	12/01/69

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS NAUTILUS	SSN 571	Regular Overhaul	01/20/64	05/01/66
USS SANDLANCE	SSN 660	New Construction	06/29/64	10/02/71
USS JOHN ADAMS	SSBN 620	Post Shakedown Availability	08/23/64	09/26/64
USS SEAWOLF	SSN 575	Refueling Overhaul	05/05/65	08/21/67
USS DACE	SSN 607	Post Shakedown Availability	09/08/65	11/22/65
USS TULLIBEE	SSN 597	Refueling Overhaul	12/20/65	11/28/68
USS TINOSA	SSN 606	Post Shakedown Availability	04/01/66	06/18/66
USS SAM HOUSTON	SSBN 609	Refueling Overhaul	08/24/66	11/22/67
USS NAUTILUS	SSN 571	Refueling Overhaul	08/15/67	12/09/68
USS JACK	SSN 605	Restricted Availability	10/11/67	12/10/67
USS ANDREW JACKSON	SSBN 619	Refueling Overhaul	03/14/68	06/14/69
USS JACK	SSN 605	Post Shakedown Availability	11/01/68	03/17/69
USS TINOSA	SSN 606	Regular Overhaul	05/06/69	12/16/71
USS SAM RAYBURN	SSBN 635	Refueling Overhaul	01/19/70	09/02/71
USS JACK	SSN 605	Restricted Availability	02/28/70	03/13/70
USS JACK	SSN 605	Regular Overhaul	02/06/71	04/27/72

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS GEORGE BANCROFT	SSBN 643	Refueling Overhaul	04/28/71	07/31/72
USS LAPON	SSN 661	Regular Overhaul	10/26/71	10/13/72
USS SAM RAYBURN	SSBN 635	Post Conversion Availability	01/11/72	02/17/72
USS HAMMERHEAD	SSN 663	Regular Overhaul	03/14/72	02/09/73
USS GREENLING	SSN 614	Restricted Availability	04/04/72	06/25/73
USS SANDLANCE	SSN 660	Post Shakedown Availability/ Restricted Availability	06/19/72	08/28/72
USS DACE	SSN 607	Restricted Availability	07/07/72	07/30/72
USS WILL ROGERS	SSBN 659	Refueling Overhaul	10/10/72	02/08/74
USS GEORGE BANCROFT	SSBN 643	Post Conversion Availability	12/21/72	01/31/73
USS TREPANG	SSN 674	Restricted Availability/ Intermediate Dry Docking	01/10/73	02/07/73
USS TULLIBEE	SSN 597	Refueling Overhaul	03/01/73	08/30/74
USS SEA DEVIL	SSN 664	Restricted Availability/ Intermediate Dry Docking	05/07/73	06/29/73
USS STURGEON	SSN 637	Restricted Availability	06/05/73	04/16/74

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS GRAYLING	SSN 646	Regular Overhaul	07/02/73	05/28/74
USS GEORGE C MARSHALL	SSBN 654	Post Conversion Availability	07/09/73	08/13/73
USS GEORGE W. CARVER	SSBN 656	Post Conversion Availability	08/20/73	09/27/73
USS FRANCIS S. KEY	SSBN 657	Post Conversion Availability	10/15/73	11/13/73
USS FLYING FISH	SSN 673	Regular Overhaul	11/15/73	11/06/74
USS JOHN ADAMS	SSBN 620	Refueling Overhaul	02/01/74	04/15/76
USS MARIANO G. VALLEJO	SSBN 658	Post Conversion Availability	05/09/74	06/12/74
USS WILL ROGERS	SSBN 659	Post Conversion Availability	06/28/74	08/09/74
USS SEA DEVIL	SSN 664	Regular Overhaul	07/01/74	06/22/75
USS TUNNY	SSN 682	Post Shakedown Availability	08/20/74	10/09/74
USS TREPANG	SSN 674	Regular Overhaul	10/15/74	10/24/75
USS BILLFISH	SSN 676	Regular Overhaul	01/13/75	12/11/75
USS GEORGE W. CARVER	SSBN 656	Restricted Availability	03/28/75	05/20/75
USS HENRY CLAY	SSBN 625	Refueling Overhaul	04/29/75	07/29/77
USS JACK	SSN 605	Refueling Overhaul	10/01/75	01/23/78

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS TECUMSEH	SSBN 628	Technical Availability	10/22/75	11/30/75
USS TREPANG	SSN 674	Restricted Availability	10/25/75	11/04/75
USS DANIEL BOONE	SSBN 629	Regular Overhaul	03/23/76	03/24/78
USS WHALE	SSN 638	Refueling Overhaul	09/15/76	07/07/78
USS JOHN ADAMS	SSBN 620	Post Shakedown Availability	09/29/76	11/03/76
USS JOHN C. CALHOUN	SSBN 630	Regular Overhaul	01/17/77	12/22/78
USS WILLIAM H. BATES	SSN 680	Selected Restricted Availability	03/07/77	05/02/77
USS RICHARD B. RUSSELL	SSN 687	Selected Restricted Availability	05/09/77	06/29/77
USS CAVALLA	SSN 684	Selected Restricted Availability	06/13/77	08/07/77
USS JAMES MADISON	SSBN 627	Extended Refit Period	09/11/77	11/07/77
USS TECUMSEH	SSBN 628	Regular Overhaul	09/27/77	06/27/79
USS HENRY CLAY	SSBN 625	Post Shakedown Availability	01/06/78	02/23/78
USS SAM RAYBURN	SSBN 635	Regular Overhaul	02/01/78	10/23/79
USS VON STEUBEN	SSBN 632	Extended Refit Period	03/10/78	05/06/78
USS CASIMIR PULASKI	SSBN 633	Extended Refit Period	05/18/78	07/17/78

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS STONEWALL JACKSON	SSBN 634	Regular Overhaul	08/07/78	03/28/80
USS SIMON BOLIVAR	SSBN 641	Regular Overhaul	03/02/79	12/28/80
USS NATHAN HALE	SSBN 623	Extended Refit Period	04/24/79	06/20/79
USS ARCHERFISH	SSN 678	Selected Restricted Availability	07/30/79	10/01/79
USS TULLIBEE	SSN 597	Refueling Overhaul	08/18/79	10/04/82
USS ALEXANDER HAMILTON	SSBN 617	Extended Refit Period	09/01/79	10/28/79
USS BENJAMIN FRANKLIN	SSBN 640	Regular Overhaul	11/12/79	09/18/81
USS TINOSA	SSN 606	Selected Restricted Availability	01/07/80	03/22/80
USS PARGO	SSN 650	Selected Restricted Availability	02/20/80	04/19/80
USS GEORGE C. MARSHALL	SSBN 654	Extended Refit Period	03/31/80	05/27/80
USS BILLFISH	SSN 676	Selected Restricted Availability	04/18/80	06/15/80
USS GEORGE BANCROFT	SSBN 643	Regular Overhaul	06/01/80	03/05/82
USS GEORGE W. CARVER	SSBN 656	Extended Refit Period	06/17/80	08/11/80
USS WHALE	SSN 638	Selected Restricted Availability	07/29/80	09/26/80
USS TREPANG	SSN 674	Regular Overhaul	11/17/80	11/16/82

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS GREENLING	SSN 614	Selected Restricted Availability	01/21/81	03/17/81
USS KAMEHAMEHA	SSBN 642	Regular Overhaul	04/01/81	12/09/82
USS PHILADELPHIA	SSN 690	Selected Restricted Availability	04/20/81	06/17/81
USS ARCHERFISH	SSN 678	Selected Restricted Availability	08/05/81	09/29/81
USS JAMES MONROE	SSBN 622	Extended Refit Period	09/20/81	11/16/81
USS JAMES K. POLK	SSBN 645	Regular Overhaul	09/30/81	04/21/83
USS TINOSA	SSN 606	Selected Restricted Availability	01/08/82	03/08/82
USS GATO	SSN 615	Selected Restricted Availability	03/09/82	05/06/82
USS BILLFISH	SSN 676	Regular Overhaul	05/19/82	11/05/83
USS ANDREW JACKSON	SSBN 619	Extended Refit Period	06/17/82	08/21/82
USS GROTON	SSN 694	Selected Restricted Availability	06/17/82	09/28/82
USS PARGO	SSN 650	Selected Restricted Availability	10/01/82	11/19/82
USS JACK	SSN 605	Regular Overhaul	10/04/82	04/08/85
NAVAL RESEARCH ONE	NR-1	Regular Overhaul	11/10/82	08/29/83

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS GREENLING	SSN 614	Selected Restricted Availability	01/11/83	03/13/83
USS DANIEL WEBSTER	SSBN 626	Extended Refit Period	02/13/83	04/09/83
USS ARCHERFISH	SSN 678	Regular Overhaul	03/01/83	10/14/84
USS WHALE	SSN 638	Selected Restricted Availability	04/15/83	06/10/83
USS TINOSA	SSN 606	Regular Overhaul	07/13/83	09/30/85
USS DACE	SSN 607	Selected Restricted Availability	10/01/83	11/30/83
USS DALLAS	SSN 700	Selected Restricted Availability	01/07/84	03/07/84
USS ULYSSES S. GRANT	SSBN 631	Refueling Overhaul	02/01/84	06/11/87
USS JAMES MONROE	SSBN 622	Extended Refit Period	03/07/84	05/05/84
USS GATO	SSN 615	Selected Restricted Availability	04/09/84	06/09/84
USS BOSTON	SSN 703	Selected Restricted Availability	06/15/84	08/15/84
USS PHILADELPHIA	SSN 690	Regular Overhaul	06/25/84	01/21/86
USS GREENLING	SSN 614	Regular Overhaul	10/01/84	10/09/87
USS ALEXANDER HAMILTON	SSBN 617	Extended Refit Period	11/07/84	01/09/85
USS SNOOK	SSN 592	Special Availability	01/15/85	03/27/85

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS SIMON BOLIVAR	SSBN 641	Refueling Overhaul	02/01/85	11/20/87
USS HENRY CLAY	SSBN 625	Extended Refit Period	03/03/85	04/28/85
USS ANDREW JACKSON	SSBN 619	Extended Refit Period	06/21/85	08/18/85
USS TREPANG	SSN 674	Selected Restricted Availability	08/01/85	09/28/85
USS DACE	SSN 607	Selected Restricted Availability	09/30/85	85/12/02
USS GROTON	SSN 694	Regular Overhaul	10/01/85	05/20/88
USS JAMES K. POLK	SSBN 645	Refueling Overhaul	01/15/86	11/29/88
USS DANIEL WEBSTER	SSBN 626	Extended Refit Period	02/28/86	04/25/86
USS BILLFISH	SSN 676	Selected Restricted Availability	05/01/86	06/28/86
USS GATO	SSN 615	Regular Overhaul	05/28/86	02/26/90
USS ARCHERFISH	SSN 678	Selected Restricted Availability	09/30/86	12/05/86
USS KAMEHAMEHA	SSBN 642	Refueling Overhaul	11/30/86	12/23/89
USS BOSTON	SSN 703	Selected Restricted Availability	01/22/87	03/22/87
USS JAMES MONROE	SSBN 622	Extended Refit Period	03/12/87	05/10/87
USS AUGUSTA	SSN 710	Selected Restricted Availability	05/22/87	07/22/87

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS LAFAYETTE	SSBN 616	Extended Refit Period	05/31/87	07/28/87
USS TINOSA	SSN 606	Selected Restricted Availability	08/03/87	10/15/87
USS SKIPJACK	SSN 585	Selected Restricted Availability	09/30/87	12/21/87
USS TULLIBEE	SSN 597	Inactivation	09/30/87	07/01/88
USS BLUEFISH	SSN 675	Refueling Overhaul	12/01/87	06/17/90
USS SCULPIN	SSN 590	Selected Restricted Availability	01/05/88	03/12/88
USS CITY OF CORPUS CHRISTI	SSN 705	Selected Restricted Availability	01/18/88	03/10/88
USS SHARK	SSN 591	Selected Restricted Availability	05/02/88	07/28/88
USS SANDLANCE	SSN 660	Regular Overhaul	06/01/88	08/08/90
USS ALBUQUERQUE	SSN 706	Selected Restricted Availability	06/13/88	08/19/88
USS PHILADELPHIA	SSN 690	Selected Restricted Availability	09/07/88	11/06/88
USS DALLAS	SSN 700	Depot Modernization Period	10/03/88	09/27/89
USS DANIEL WEBSTER	SSBN 626	Intermediate Dry Docking	02/24/89	03/20/89
USS TREPANG	SSN 674	Refueling Overhaul	03/01/89	11/01/91

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS BOSTON	SSN 703	Depot Modernization Period	06/15/89	05/18/90
USS JACK	SSN 605	Inactivation	10/01/89	07/27/90
USS GEORGE W. CARVER	SSBN 656	Extended Refit Period	10/18/89	12/16/89
USS GREENLING	SSN 614	Selected Restricted Availability	01/10/90	03/18/90
USS CITY OF CORPUS CHRISTI	SSN 705	Depot Modernization Period	03/01/90	03/10/91
USS TINOSA	SSN 606	Selected Restricted Availability	03/12/90	05/06/90
USS L. MENDEL RIVERS	SSN 686	Refueling Overhaul	05/07/90	06/05/93
USS LAFAYETTE	SSBN 616	Extended Refit Period	06/05/90	08/03/90
USS PITTSBURGH	SSN 720	Selected Restricted Availability	09/04/90	10/18/90
USS ALBUQUERQUE	SSN 706	Depot Modernization Period	10/01/90	07/19/91
NAVAL RESEARCH ONE	NR-1	Refueling Overhaul	11/06/90	11/29/92
USS NORFOLK	SSN 714	Depot Modernization Period	02/27/91	05/01/92
USS WILL ROGERS	SSBN 659	Extended Refit Period	06/24/91	08/21/91
USS DANIEL BOONE	SSBN 629	Extended Refit Period	07/12/91	09/05/91
USS TECUMSEH	SSBN 628	Extended Refit Period	09/09/91	11/01/91

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS FINBACK	SSN 670	Selected Restricted Availability	09/30/91	11/27/91
USS MINNEAPOLIS/ST. PAUL	SSN 708	Depot Modernization Period	09/30/91	09/01/92
USS SILVERSIDES	SSN 679	Selected Restricted Availability	11/20/91	02/07/92
USS PARGO	SSN 650	Selected Restricted Availability	01/06/92	02/29/92
USS GATO	SSN 615	Selected Restricted Availability	03/02/92	04/29/92
USS HAMMERHEAD	SSN 663	Selected Restricted Availability	03/23/92	05/19/92
USS CINCINNATI	SSN 693	Selected Restricted Availability	05/19/92	07/21/92
USS AUGUSTA	SSN 710	Depot Modernization Period	06/01/92	10/23/93
USS GREENLING	SSN 614	Selected Restricted Availability	06/30/92	08/27/92
USS PHOENIX	SSN 702	Selected Restricted Availability	08/10/92	11/01/92
USS PHILADELPHIA	SSN 690	Engineered Refueling Overhaul	10/01/92	12/23/94
USS WHALE	SSN 638	Selected Restricted Availability	03/01/93	04/25/93

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS PITTSBURGH	SSN 720	Depot Modernization Period	05/03/93	08/29/94
USS ARCHERFISH	SSN 678	Selected Restricted Availability	06/01/93	07/24/93
NAVAL RESEARCH ONE	NR-1	Restricted Availability	08/09/93	10/12/93
USS MEMPHIS	SSN 691	Engineered Refueling Overhaul	02/07/94	08/06/96
USS TREPANG	SSN 674	Selected Restricted Availability	10/03/94	12/01/94
USS GRAYLING	SSN 646	Selected Restricted Availability	01/09/95	03/08/95
USS ALEXANDRIA	SSN 757	Selected Restricted Availability	01/09/95	03/15/95
USS OMAHA	SSN 692	Inactivation	02/07/95	01/31/96
USS ASHEVILLE	SSN 758	Selected Restricted Availability	03/10/95	05/23/95
USS LA JOLLA	SSN 701	Selected Restricted Availability	05/10/95	07/20/95
USS SALT LAKE CITY	SSN 716	Selected Restricted Availability	06/28/95	09/25/95
USS JEFFERSON CITY	SSN 759	Selected Restricted Availability	08/16/95	11/14/95
USS DALLAS	SSN 700	Engineered Refueling Overhaul	10/23/95	02/12/98

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS ARCHERFISH	SSN 678	Selected Restricted Availability	01/22/96	03/25/96
USS POGY	SSN 647	Selected Restricted Availability	02/01/96	04/01/96
USS BOISE	SSN 764	Intermediate Maintenance Availability	02/26/96	03/28/96
USS NEW YORK CITY	SSN 696	Inactivation	03/19/96	07/10/97
USS AUGUSTA	SSN 710	Selected Restricted Availability	04/08/96	06/15/96
USS MONTPELIER	SSN 765	Intermediate Maintenance Availability	06/06/96	07/15/96
USS PHOENIX PHASE I	SSN 702	Intermediate Maintenance Availability	06/11/96	06/25/96
USS MINNEAPOLIS ST. PAUL	SSN 708	Intermediate Maintenance Availability	07/15/96	08/16/96
USS PHOENIX PHASE II	SSN 702	Intermediate Maintenance Availability	07/22/96	08/23/96
NAVAL RESEARCH ONE	NR-1	Selected Restricted Availability	08/06/96	10/18/96
USS SCRANTON	SSN 756	Intermediate Maintenance Availability	08/12/96	09/13/96
USS ALBANY	SSN 753	Intermediate Maintenance Availability	09/16/96	10/25/96
USS GROTON	SSN 694	Inactivation	10/01/96	03/30/98

**Portsmouth Naval Shipyard
History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS TREPANG	SSN 674	Selected Restricted Availability	10/15/96	12/13/96
USS PROVIDENCE	SSN 719	Selected Restricted Availability	10/17/96	12/21/96
USS ATLANTA	SSN 712	Intermediate Maintenance Availability	10/28/96	11/22/96
USS OKLAHOMA CITY	SSN 723	Intermediate Maintenance Availability	10/28/96	11/22/96
USS OKLAHOMA CITY	SSN 723	Depot Modernization Period	01/06/97	03/18/98
USS RICKOVER	SSN 709	Intermediate Maintenance Availability	01/13/97	03/13/97
USS MINNEAPOLIS SAINT PAUL	SSN 708	Intermediate Maintenance Availability	01/27/97	02/28/97
USS SPRINGFIELD	SSN 761	Selected Restricted Availability	02/03/97	04/04/97
USS CITY OF CORPUS CHRISTI	SSN 705	Selected Restricted Availability	04/01/97	05/31/97
USS NARWHAL	SSN 671	Intermediate Maintenance Availability	05/26/97	06/30/97
USS NORFOLK	SSN 714	Intermediate Maintenance Availability	05/27/97	06/30/97
USS HOUSTON	SSN 713	Selected Restricted Availability	06/30/97	09/29/97

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History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS SAN JUAN	SSN 751	Intermediate Dry Docking	08/01/97	09/24/97
USS ALBUQUERQUE	SSN 706	Selected Restricted Availability	10/01/97	12/08/97
USS PHOENIX	SSN 702	Inactivation	10/01/97	03/17/99
USS MIAMI	SSN 755	Selected Restricted Availability	10/15/97	01/23/98
USS PITTSBURGH	SSN 720	Selected Restricted Availability	11/15/97	02/04/98
USS NORFOLK	SSN 714	Selected Restricted Availability	03/02/98	05/13/98
USS HELENA	SSN 725	Depot Modernization Period	03/09/98	04/01/99
USS PHILADELPHIA	SSN 690	Selected Restricted Availability	06/09/98	10/08/98
NAVAL RESEARCH ONE	NR-1	Selected Restricted Availability	08/05/98	11/03/98
USS LA JOLLA	SSN 701	Engineered Refueling Overhaul	10/01/98	12/09/00
USS ALEXANDRIA	SSN 757	Selected Restricted Availability	10/05/98	12/02/98
USS MINNEAPOLIS SAINT PAUL	SSN 708	Selected Restricted Availability	01/28/99	04/23/99
USS SALT LAKE CITY	SSN 716	Selected Restricted Availability	03/02/99	05/02/99

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History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS HARTFORD	SSN 768	Selected Restricted Availability	05/01/99	07/16/99
USS SPRINGFIELD	SSN 761	Intermediate Maintenance Availability	05/10/99	06/18/99
USS TOLEDO	SSN 769	Selected Restricted Availability	07/21/99	10/14/99
USS SAN JUAN	SSN 751	Intermediate Maintenance Availability	09/01/99	09/30/99
USS HAMPTON	SSN 767	Intermediate Maintenance Availability	09/07/99	09/30/99
USS ANNAPOLIS	SSN 760	Selected Restricted Availability	09/29/99	12/20/99
USS SAN JUAN	SSN 751	Depot Modernization Period	10/01/99	12/14/00
USS AUGUSTA	SSN 710	Selected Restricted Availability	11/23/99	02/10/00
USS CITY OF CORPUS CHRISTI	SSN 705	Engineered Refueling Overhaul	03/31/00	03/25/02
USS PROVIDENCE	SSN 719	Selected Restricted Availability	05/09/00	07/29/00
USS SPRINGFIELD	SSN 761	Selected Restricted Availability	10/02/00	12/10/01
NAVAL RESEARCH ONE	NR-1	Selected Restricted Availability	11/28/00	04/04/01

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History Of Nuclear Submarines**

New Construction, Overhauls And Scheduled Maintenance Availabilities

Nuclear Submarine Name	Submarine Number	Type Availability	Availability Start Date	Availability Comp Date
USS MIAMI	SSN 755	Depot Modernization Period	01/31/01	02/11/02
USS ALBUQUERQUE	SSN 706	Engineered Refueling Overhaul	07/01/01	
USS ALEXANDRIA	SSN 757	Depot Modernization Period	01/31/02	
USS MEMPHIS	SSN 691	Red. Gear Repl. Technical Availability	03/13/02	12/11/02
USS CITY OF CORPUS CHRISTI	SSN 705	C4I Upgrade Technical Availability	05/23/02	
USS MEMPHIS	SSN 691	Selected Restricted Availability	07/15/02	12/11/02
USS NORFOLK	SSN 714	Engineered Refueling Overhaul	10/15/02	
USS PHILADELPHIA	SSN 690	Selected Restricted Availability	10/01/02	
USS HARTFORD	SSN 768	Selected Restricted Availability	01/07/03	
USS ANNAPOLIS	SSN 760	Depot Modernization Period	04/29/02	

Appendix E

Non-Work-Related Medical X-Ray Examinations Given at PNS

Frequency and Location of Non-Work-Related Medical X-Ray Examinations Given at PNS (Adapted from Daniels et al., 2004b)			
Body Location	Frequency	Percent	Cumulative Frequency
Chest	196	27.48	196
Lumbar-Sacral Spine	65	9.11	261
Thoracic Spine	3	0.42	264
Cervical Spine	18	2.52	282
Hand, Wrist, or Finger	146	20.47	428
Leg	26	3.64	454
Arm	6	0.84	460
Skull	14	1.96	474
Barium Enema	1	0.14	475
Upper GI	3	0.42	478
Abdomen	3	0.42	481
Knee	47	6.59	528
Shoulder	34	4.76	562
Foot, Toe, Ankle	86	12.06	648
Hip, Pelvis	6	0.84	654
Elbow	54	7.57	708
Facial Bones	2	0.28	710
Clavicle	1	0.14	711
Sternum	1	0.14	712
Coccyx	1	0.14	713

Appendix F


Actual and Estimated Routine and Diagnostic Medical X-Rays Combined Given at PNS

Frequency and Location of Actual and Estimated Routine and Diagnostic Medical X-Rays Combined Given at PNS (Adapted from Daniels et al., 2004b)						
Body Location	Frequency	Percent	Cumulative Frequency	Estimated Bone Marrow Dose Per Exam mSv		
				Chest Photo*	Chest Direct†	Chest MX‡
Chest	2,804	84.38	2,804	1.50	0.04	0.07
Lumbar-Sacral Spine	70	2.10	2,874		2.29	
Thoracic Spine	3	0.09	2,877		0.94	
Cervical Spine	18	0.54	2,895		0.15	
Hand, Wrist, or Finger	146	4.39	3,041	Not Calculated		
Leg	26	0.78	3,067	Not Calculated		
Arm	6	0.18	3,073	Not Calculated		
Skull	14	0.42	3,087		0.31	
Barium Enema	1	0.03	3,088		4.72	
Upper GI	3	0.09	3,091		3.34	
Abdomen	3	0.09	3,094		0.72	
Knee	47	1.41	3,138	Not Calculated		
Shoulder	34	1.023	3,172		0.08	
Foot, Toe, Ankle	86	2.58	3,258			
Hip, Pelvis	6	0.18	3,264		0.46	
Elbow	54	1.62	3,318	Not Calculated		
Facial Bones	2	0.06	3,320	Not Calculated		
Clavicle	1	0.03	3,321	Not Calculated		
Sternum	1	0.03	3,322		0.98	
Coccyx	1	0.03	3,323		1.22	

* Chest Work-Related Photofluorograph
† Chest Work-Related Direct Radiography (Single View)
‡ Chest Multi Projection

Appendix G

Benzene Document

 AAM PORTSMOUTH NAVAL SHIPYARD PORTSMOUTH, N. H. 730 *ada* IN REPLY REFER TO NO. 470 M2-4

MAR 24 1958

MEMORANDUM

From: 400
To: 700

Subj: Industrial hygiene survey of Shop 02; action concerning

Ref: (a) 700 memo 731 of 24 Feb 1958

1. Paragraph 7 of reference (a) made several recommendations concerning industrial hygiene conditions in Building 154. The following action has been taken:

a. Stoddard Solvent, Stock #W6850-264-9038 has been substituted for kerosene. The use of benzene has been discontinued.

b. All new materials will be submitted to the Industrial Hygiene Division for toxicological evaluation before being placed in use.

c. The exhaust system for the fork-lift and automotive maintenance system has been inspected and cleaned. Several cleaning rags had been sucked into the system thus impairing its efficiency. These have been removed and the system is now of ample capacity.

d. An estimate has been prepared for the installation of a general ventilation system in Building 154. The cost of such a system is rather high, but the work will be performed as soon as practicable.

e. Work is now underway to provide an extension for the exhaust fan in the injector room to carry oil mist outside the building.

f. Ear plugs have been provided to all employees and they are being worn at the employees' discretion pending designation of noise hazardous operations.

g. A work request has been submitted to repair the carbon monoxide alarms and place them in operation. This should be accomplished by 1 May 1958.

W.M. Gordon
W. M. GORDON

Date of Memo
March 24, 1958

Note that the
use of
Benzene has
been
discontinued

Carbon Tetrachloride Document

In reply address not the number of this letter but the Medical Officer, Naval Shipyard, Portsmouth, N. H.

Refer to No:

MEDICAL DEPARTMENT
U. S. NAVAL SHIPYARD

Portsmouth, N. H.

27 February 27, 1948



Date of the Memo
February 27,
1948

From: Industrial Hygienist
To: Supply Officer

Subj: Trichloroethylene, Request for Initial Supply.

1. It is requested that an initial supply of trichloroethylene, Stock No. 812651, be established.
2. For reasons of health, this solvent is a suitable substitute for carbon tetrachloride.
3. It is estimated that 100 gallons would be a six months supply. Carbon tetrachloride should be decreased by the same amount.

Note that Trichloroethylene has been substituted for Carbon Tetrachloride

JAMES E. FULLER

Appendix H

Table 1: Illustration of Shop/Job Title Collapse Using Painters

Job Title Collapse

Jobs Titles Associated with Painting Group (03)

Painter	Painter Helper
Painter Apprentice	Painter Supervisor
Painter Worker	Painting Foreman General

Production Shop

Paint Shops (71)

71	271
071	371
171	

+

Painting Group (03)

Painter
Painter Helper
Painter Apprentice
Painter Worker
Painting Foreman General

Shop/Job/Code

= **7103**

Exposed
Job title with potential solvent exposure assigned to a production shop where exposure was likely to occur.

Support Shop

Maintenance Shops (07)

07
007
207

+

Painting Group (03)

Painter
Painter Helper
Painter Apprentice
Painter Worker
Painting Foreman General

= **0703**

Shop/Job/Code

Exposed
Job title with potential solvent exposure assigned to a support shop where exposure was likely to occur.

Administrative Shop

Planning & Estimating Shops (04)

04	90	322
20	93	368
22	222	373
24	278	393
25	293	395
44	320	396
86	321	801

+

Painting Group (03)

Painter
Painter Helper
Painter Apprentice
Painter Supervisor
Painter Worker
Painting Foreman General

= **0403**

Shop/Job/Code

Not Exposed
Job title with potential solvent exposure but assigned to an administrative shop where exposure were not likely to occur.

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Welding Group	01x	Flame/Arc Cutter	Flame Cutter
Welding Group	01x	Flame/Arc Cutter	Gas Cutter/Burner
Welding Group	01x	Gas Generating Plant Operator	Gas Plant Operator
Welding Group	01x	Industrial Equipment Mechanic	Mechanic (Learner)
Welding Group	01x	Metal Processing	Shielding Installer
Welding Group	01x	Metal Processing	Struct Shop Gen Fmn
Welding Group	01x	Welder	Electric Welder
Welding Group	01x	Welder	Electric Welder Leadingman
Welding Group	01x	Welder	Electric Welder Leadingman Spec
Welding Group	01x	Welder	Electric Welder Quarterman
Welding Group	01x	Welder	Electric Welder Snapper
Welding Group	01x	Welder	Foreman Welder
Welding Group	01x	Welder	Foreman Welder Electric
Welding Group	01x	Welder	Gas Welder
Welding Group	01x	Welder	Operator(Acetylene)
Welding Group	01x	Welder	Welder
Welding Group	01x	Welder	Welder (Electric)

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Welding Group	01x	Welder	Welder (Limited)
Welding Group	01x	Welder	Welder Apprentice
Welding Group	01x	Welder	Welder Combination Apprentice
Welding Group	01x	Welder	Welder Foreman
Welding Group	01x	Welder	Welder General Foreman
Welding Group	01x	Welder	Welder Helper
Welding Group	01x	Welder	Welder Instructor
Welding Group	01x	Welder	Welder Leadingman
Welding Group	01x	Welder	Welder Limited
Welding Group	01x	Welder	Welder Quarterman
Welding Group	01x	Welder	Welder Special
Welding Group	01x	Welder	Welder Trainee
Welding Group	01x	Welder	Welding Worker
Transportation Group	02x	Equipment Cleaner	Equipment Cleaner
Transportation Group	02x	Equipment Cleaner	Equipment Cleaner Foreman
Transportation Group	02x	Equipment Cleaner	Equipment Cleaner General Foreman
Transportation Group	02x	Equipment Cleaner	Equipment Cleaner Leader
Transportation Group	02x	Equipment Cleaner	Equipment Cleaner Leader Trainee
Transportation Group	02x	Laborer	Laborer (Cleaner)
Transportation Group	02x	Laborer	Laborer (Cleaner) Leadingman Foreman

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Transportation Group	02x	Laborer	Laborer Leadingman (Cleaner)
Transportation Group	02x	Laborer	Laborer/Cleaner
Transportation Group	02x	Laborer	Laborer/Cleaner Leadingman Foreman
Transportation Group	04x	Equipment Cleaner	Component Cleaner
Transportation Group	04x	Equipment Cleaner	Tank Cleaner
Transportation Group	16x	Fork Lift Operator	High Lift Truck Operator
Transportation Group	16x	Fork Lift Operator	Operator High Lift Truck
Transportation Group	38x	Automotive Mechanic	Automotive Mechanic
Transportation Group	39x	Crane Operator	Crane Operator
Transportation Group	39x	Crane Operator	Crane Operator Trainee
Transportation Group	39x	Crane Operator	Operating Engineer (Hoisting Equip)
Transportation Group	39x	Crane Operator	Operating Engineer Foreman/Ldgman
Transportation Group	39x	Crane Operator	Operating Engineer (Hoisting Equipment)
Transportation Group	40x	Motor Vehicle Operator	Chauffeur

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Transportation Group	40x	Motor Vehicle Operator	Chauffeur (Heavy Duty)
Transportation Group	40x	Motor Vehicle Operator	Motor Vehicle Operator
Transportation Group	40x	Motor Vehicle Operator	Truck Driver
Transportation Group	40x	Motor Vehicle Operator	Truck Driver (Heavy)
Transportation Group	42x	Locomotive Engineer	Engineman
Transportation Group	42x	Locomotive Engineer	Engineman (Hoist/Portable)
Transportation Group	43x	Oiler & Greaser	Oiler
Transportation Group	50x	Fuel Distribution System Operator	Liquid Fuel Distributing System Operator
Transportation Group	50x	Fuel Distribution System Operator	Liquid Fuel Pump Operator
Painting Group	03x	Painter	Painter
Painting Group	03x	Painter	Painter Apprentice
Painting Group	03x	Painter	Painter Foreman General
Painting Group	03x	Painter	Painter Helper
Painting Group	03x	Painter	Painting Worker

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Electrician Group	21x	Rubber Products Molder	Rubber Worker
Electrician Group	27x	Electronics Mechanic	Electronics Mechanic
Electrician Group	27x	Electronics Mechanic	Electronics Mechanic Apprentice
Electrician Group	27x	Electronics Mechanic	Electronics Mechanic Helper
Electrician Group	27x	Electronics Mechanic	Instrument Maker
Electrician Group	27x	Electronics Mechanic	Instrument Mech (Electronic)
Electrician Group	27x	Electronics Mechanic	Radio Mechanic
Electrician Group	27x	Electronics Mechanic	Radio Mechanic (Layer Out)
Electrician Group	27x	Electronics Mechanic	Radio Mechanic (Limited)
Electrician Group	41x	Electric Power Controller	Electric Power Control
Electrician Group	41x	Electric Power Controller	Power Plant Control man (Hp)
Electrician Group	41x	Electrician	Electrician
Electrician Group	41x	Electrician	Electrician (Apsp)
Electrician Group	41x	Electrician	Electrician (Power Plant)
Electrician Group	41x	Electrician	Electrician Apprentice
Electrician Group	41x	Electrician	Electrician Foreman

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Electrician Group	41x	Electrician	Electrician Foreman (General)
Electrician Group	41x	Electrician	Electrician Foreman Leadingman
Electrician Group	41x	Electrician	Electrician General Foreman
Electrician Group	41x	Electrician	Electrician Helper
Electrician Group	41x	Electrician	Electrician Instructor
Electrician Group	41x	Electrician	Electrician Leadingman
Electrician Group	41x	Electrician	Electrician Limited
Electrician Group	41x	Electrician	Electrician Quarterman
Electrician Group	41x	Electrician	Foreman General Electric
Electrician Group	41x	Electrician	Helper Electrician
Electrician Group	41x	Electrician	Wireman
Electrician Group	73x	Electronics Technician	Electronics Technician
Electrician Group	73x	Electronics Technician	Electronics Technician (Instrument)
Electrician Group	73x	Electronics Technician	Elex Tech
Electrician Group	73x	Electronics Technician	Elex Tech (Instrum)
Machining Group	13x	Metal Worker	Flange Turner
Machining Group	22x	Machinist	Inside Machinist
Machining Group	22x	Machinist	Ldman Machinist Inside
Machining Group	22x	Machinist	Machinist (Inside)
Machining Group	22x	Machinist	Machinist (Inside)

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Machining Group	22x	Metal Forming Machine Operator	Mach Operator
Machining Group	22x	Metal Forming Machine Operator	Machine Operator
Machining Group	22x	Metal Forming Machine Operator	Machine Tool Operator
Machining Group	22x	Tool Grinder	Foreman Ldgmn Tool/Cutter Gr
Machining Group	22x	Tool Grinder	Tool & Cutter Grinder
Machining Group	22x	Tool Grinder	Tool/Cutter Grinder
Machining Group	22x	Tool Grinder	Tool/Cutter Grinder Foreman
Machining Group	22x	Toolmaker	Toolmaker
Machining Group	22x	Toolmaker	Toolmaker Leadingman
Machining Group	26x	Industrial Equipment Mechanic	Equipment Mechanic
Machining Group	26x	Industrial Equipment Mechanic	Equipment Mechanic (Heavy Duty)
Machining Group	26x	Industrial Equipment Mechanic	Equipment Mechanic Foreman
Machining Group	26x	Industrial Equipment Mechanic	Equipment Repairer
Machining Group	26x	Industrial Equipment Mechanic	Mechanic Master (Outfitting Group)

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Machining Group	26x	Machinist	Foreman (Ldm) Machinist
Machining Group	26x	Machinist	Leadingman Machinist
Machining Group	26x	Machinist	Machinery Worker
Machining Group	26x	Machinist	Machinist
Machining Group	26x	Machinist	Machinist Leadingman
Machining Group	26x	Machinist	Machinist Leadingman (Marine)
Machining Group	26x	Machinist	Machinist Leadingman Inside
Machining Group	26x	Machinist	Machinist (Maintenance)
Machining Group	26x	Machinist	Machinist (Maintenance)
Machining Group	26x	Machinist	Machinist (Maintenance) Foreman
Machining Group	26x	Machinist	Machinist (Maintenance) Gen Foreman
Machining Group	26x	Machinist	Machinist (Maintenance) Ldgmn/Frman
Machining Group	26x	Machinist	Machinist (Maintenance) Leadingman
Machining Group	26x	Machinist	Machinist (Marine)
Machining Group	26x	Machinist	Machinist (Marine) Leadingman
Machining Group	26x	Machinist	Machinist (Marine) Apprentice
Machining Group	26x	Machinist	Machinist (Marine) Foreman Leadingman
Machining Group	26x	Machinist	Machinist (Marine) General Foreman
Machining Group	26x	Machinist	Machinist (Marine) Helper

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Machining Group	26x	Machinist	Machinist (Marine) Leadingman
Machining Group	26x	Machinist	Machinist (Marine) Master
Machining Group	26x	Machinist	Machinist (Marine) Quarterman
Machining Group	26x	Machinist	Machinist (Outside)
Machining Group	26x	Machinist	Machinist (Outside) Master
Machining Group	26x	Machinist	Machinist (Repair Shops) Gen Foreman
Machining Group	26x	Machinist	Machinist Apprentice
Machining Group	26x	Machinist	Machinist Foreman
Machining Group	26x	Machinist	Machinist Foreman Maintenance
Machining Group	26x	Machinist	Machinist Foreman/Leadingman
Machining Group	26x	Machinist	Machinist General Foreman (Marine)
Machining Group	26x	Machinist	Machinist General Foreman Maintenance
Machining Group	26x	Machinist	Machinist Helper
Machining Group	26x	Machinist	Machinist Helper (Marine)
Machining Group	26x	Machinist	Machinist Instructor
Machining Group	26x	Machinist	Machinist Leadingman
Machining Group	26x	Machinist	Machinist Leadingman (Marine)
Machining Group	26x	Machinist	Machinist Limited
Machining Group	26x	Machinist	Machinist Marine
Machining Group	26x	Machinist	Machinist Marine Leadingman

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Machining Group	26x	Machinist	Machinist Marine Quarterman
Machining Group	26x	Machinist	Machinist Master (Marine)
Machining Group	26x	Machinist	Machinist Mechanic (Marine) Apprentice
Machining Group	26x	Machinist	Machinist Outside
Machining Group	26x	Machinist	Machinist Progressman
Machining Group	26x	Machinist	Machinist Quarterman
Machining Group	26x	Machinist	Machinist Quarterman (Chief)
Machining Group	26x	Machinist	Machinist Quarterman Inside
Machining Group	26x	Machinist	Machinist Snapper
Machining Group	26x	Machinist	Maintenance Machinist
Machining Group	26x	Machinist	Marine Machinery Mach
Machining Group	26x	Machinist	MMM Foreman
Machining Group	26x	Machinist	Quarterman Machinist (Marine)
Machining Group	26x	Machinist	Special Duties
Machining Group	26x	Marine Machinery Mechanic	Equip Mech Instr (Mach Marine)
Machining Group	26x	Marine Machinery Mechanic	Equipment Mechanic (Mach Marine)
Machining Group	26x	Marine Machinery Mechanic	Equipment Mechanic (Machinist Marine)
Machining Group	26x	Marine Machinery Mechanic	Equipment Mechanic Foreman (Mach Marine)

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Machining Group	26x	Marine Machinery Mechanic	Maintenance
Machining Group	26x	Marine Machinery Mechanic	Maintenance Foreman
Machining Group	26x	Marine Machinery Mechanic	Marine Equip Mechanic
Machining Group	26x	Marine Machinery Mechanic	Marine Equip Mechanic Instructor
Machining Group	26x	Marine Machinery Mechanic	Marine Machinery Mechanic
Machining Group	26x	Marine Machinery Mechanic	Marine Machinery Mechanic Foreman
Machining Group	26x	Marine Machinery Mechanic	Marine Machinery Repairer
Machining Group	26x	Marine Machinery Mechanic	Mechanic Ship Maintenance
Machining Group	26x	Marine Machinery Mechanic	MM Repairer
Machining Group	26x	Ships Planner, Analyst, & Progressman	Progressman (Machinist)

Table 2: Exposed Job And Shop Collapse

NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Machining Group	32x	Maintenance Mechanic	Ship Maintenance Mechanic
Machining Group	32x	Maintenance Mechanic	Ship Maintenance Mechanic
Machining Group	58x	Tool & Equipment Repairing	Tool Room Mechanic
Machining Group	58x	Tool & Equipment Repairing	Tool Room Mechanic Helper
Machining Group	58x	Tools & Parts Attending	Tool/Parts Attendant
Machining Group	58x	Tools & Parts Attending	Tool Room Attendant
Machining Group	58x	Tools & Parts Attending	Tool Room Keeper
Machining Group	58x	Tools & Parts Attending	Tools/Parts Attendant
Wood Working Group	19x	Wood Crafter	Joiner
Wood Working Group	19x	Wood Crafter	Joiner Apprentice
Wood Working Group	19x	Wood Crafter	Joiner Helper
Wood Working Group	19x	Wood Crafter	Joiner Leadingman
Wood Working Group	19x	Wood Crafter	Joiner Leadingman/Foreman
Wood Working Group	19x	Wood Crafter	Joiner Quarterman

Table 2: Exposed Job And Shop Collapse

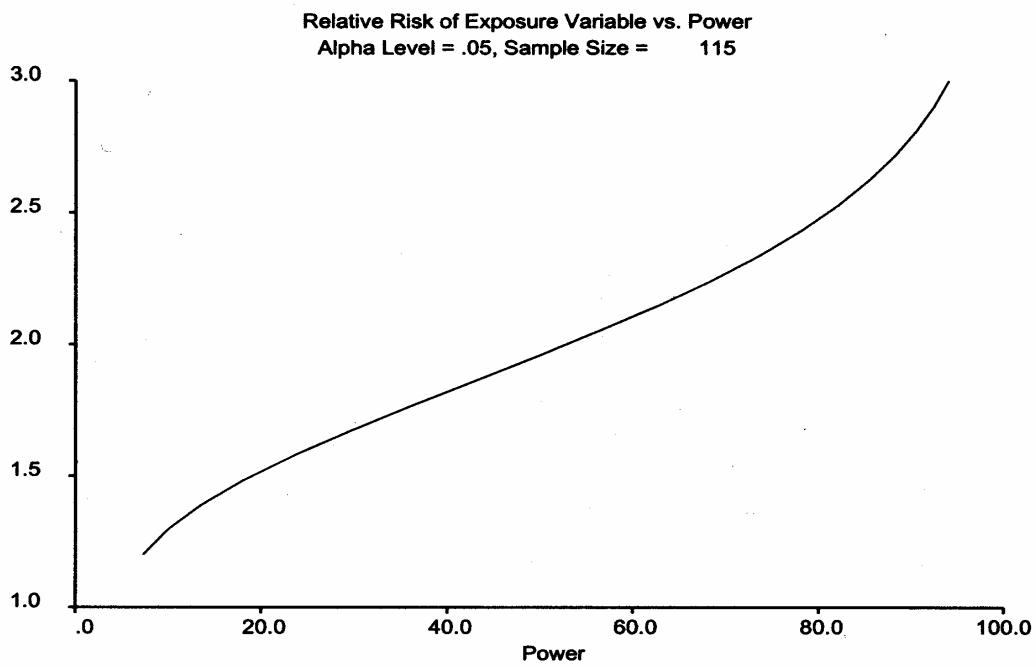
NIOSH Exposure Category	NIOSH Assigned Job Code	NIOSH Assigned Job Title	Original Site Job Title
Wood Working Group	19x	Wood Worker	Helper Woodworker
Wood Working Group	19x	Wood Worker	Woodworker
Wood Working Group	19x	Wood Worker	Woodworker Helper
Wood Working Group	19x	Wood Worker	Woodworker Leader
Wood Working Group	64x	Molder	Leader Molder
Wood Working Group	64x	Molder	Leaderman Molder
Wood Working Group	64x	Molder	Molder
Wood Working Group	64x	Molder	Molder Helper
Wood Working Group	66x	Patternmaker	Patternmaker
Wood Working Group	66x	Patternmaker	Patternmaker Apprentice

Appendix I

Power Curve Graphic

Alpha Level = 0.05

Sample Size = 115 Risk Sets



Appendix J

Place of Birth	Frequency	Percent	Cumulative Frequency
Canada	3	2.61	3
Colorado	1	0.87	4
France	1	0.87	5
Holland	1	0.87	6
Jamaica	1	0.87	7
Maine	40	34.78	47
Mass.	20	17.39	67
New Hampshire	34	29.57	101
New Jersey	1	0.87	102
New York	1	0.87	103
Panama	1	0.87	104
Pennsylvania	3	2.61	107
Poland	1	0.87	108
Rhode Island	2	1.74	110
Scotland	1	0.87	111
Virginia	1	0.87	112
Vermont	2	1.74	114
Washington State	1	0.87	115

Table 2: States Where Cases Died ($n=115$)			
State	Frequency	Percent	Cumulative Frequency
California	3	2.61	3
Connecticut	2	1.74	5
Washington, D.C.	1	0.87	6
Florida	7	6.09	13
Massachusetts	19	16.52	32
Maine	36	31.30	68
New Hampshire	43	37.39	111
Ohio	1	0.87	112
Pennsylvania	1	0.87	113
Vermont	1	0.87	114
Washington State	1	0.87	115

Appendix K

Table 1: Cumulative Bone Marrow Dose from Offsite Sources					
Number of Cases and Controls	Mean (mSv)	Median (mSv)	Min (mSv)	Max (mSv)	Collective BMD (person-mSv)
3 Controls Only	2.54	3.37	0.63	3.63	7.63

Table 2: Estimated Missed Cumulative Bone Marrow Dose					
Number of Cases and Controls	Mean (mSv)	Median (mSv)	Min (mSv)	Max (mSv)	Total (mSv)
175 (Cases & Controls)	0.35	0.16	0.02	2.54	60.92
30 (Cases Only)	0.38	0.15	0.02	2.45	11.25
145 (Controls Only)	0.34	0.16	0.02	2.54	49.67

Table 3: Full Model with 2—Way Interactions and Main Effects—Badge Exposure—Two Year Lag

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Odds Ratio	95% Confidence Limits	
On & Offsite Miss Badge Cumulative Exposure - Lagged 2 Years (1 mSv)	1	0.0108	0.0049	4.965	0.0259	1.01	1.00	1.02
Gender (1=Female, 0=Male)	1	-1.172	0.6186	3.589	0.0582	0.31	0.09	1.04
Radiation Worker (1=Yes, 0=No) Lagged 2 yrs	1	-0.7380	0.3562	4.293	0.0383	0.48	0.24	0.96
Solvent Duration Exposed - Lagged 2 Years	1	0.0436	0.0150	8.470	0.0036	1.05	1.01	1.08
TSLE is \geq 5 year and <10 years	1	-0.1684	0.3617	0.2170	0.6414	0.85	0.42	1.72
TSLE is \geq 2.5 years and <5 years	1	0.6310	0.4077	2.396	0.1216	1.88	0.85	4.18
TSLE is \geq 0 years and <2.5 years	1	-0.5678	0.4148	1.8748	0.1710	0.57	0.25	1.28
On & Offsite Badge Cumulative Exposure * Solvent Duration Exposure	1	-0.000318	0.0004	0.6389	0.4241	1.000	0.99	1.00
Radiation Worker * Solvent Duration Exposed	1	-0.0123	0.0264	0.2160	0.6421	0.99	0.94	1.04

Table 4: Reduced Model—2-way Exposure Interaction and Main Effects—Badge Exposure—Two Year Lag								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Odds Ratio	95% Confidence Limits	
On & Offsite Miss Badge Cum Exposure - Lagged 2 Years (1 mSv)	1	0.0116	0.0046	6.362	0.0117	1.01	1.00	1.02
Gender (1=Female 0=Male)	1	-1.196	0.6158	3.770	0.0522	0.30	0.09	1.01
Radiation Worker (1=Yes, 0=No) Lagged 2 yrs.	1	-0.8470	0.2734	9.600	0.0019	0.43	0.25	0.73
Solvent Duration Exposure Lagged 2 Years	1	0.0398	0.0125	10.09	0.0015	1.04	1.02	1.07
TSLE is ≥ 5 year and <10 years	1	-0.1713	0.3617	0.2241	0.6359	0.84	0.42	1.71
TSLE is ≥ 2.5 years and <5 years	1	0.6315	0.4074	2.403	0.1211	1.88	0.85	4.18
TSLE is ≥ 0 years and <2.5 years	1	-0.56137	0.4148	1.831	0.1760	0.57	0.25	1.29
On & Offsite Badge Cum Exposure - Lagged 2 Years * Solvent Duration Exposure - Lagged 2 Years	1	-0.0004	0.0004	1.176	0.2781	1.00	0.99	1.00

Table 5: Percent Change in the Radiation Exposure Variable When Other Main Effect Variables are Excluded		
Variable	Parameter Estimate	Percent Change
On & Offsite Miss Badge Cum Exposure - Lagged 2 Years—Parameter Estimate with all Variables in the Model	0.00816	
Parameter Estimate Excluding Gender	0.00815	.12
Parameter Estimate Excluding Radiation Worker Status	0.00349	.80
Parameter Estimate Excluding Solvent Duration	0.007624	.07
Parameter Estimate Excluding TSLE	0.00762	.07

Table 6: Pearson Correlation Coefficients (<i>p</i> -value)—Main Effects Model—Two-Year Lag								
On & Offsite Badge Cum Dose - Lagged 2 Years (1mSv)	Gender	Radiation Worker	CASE	Solvent Duration	TSLE ≥ 5 year and <10 years	TSLE ≥ 2.5 years and <5 years	TSLE ≥ 0 years and <2.5 years	
On & Offsite Miss Badge Cum Dose - Lagged 2 Years	-0.0804	0.3873	0.0596	0.0617	-0.0150	0.0295	0.0129	
Gender (1= Female, 0= Male)	1.000	<.0001	0.1537	0.1394	0.7193	0.4806	0.7581	
Radiation Worker (1=Yes, 0=No)	-0.0804	1.000	-0.2076	-0.1883	0.0578	-0.0036	0.0049	
CASE IDENTIFIER (1=CASE, 0=CONTROL)	0.0540	<.0001	1.000	<.0001	0.1664	0.9317	0.9066	
Solvent Duration Exposed	0.3873	-0.2076	-0.0548	0.2003	0.0225	0.0757	-0.0533	
TSLE is ≥ 5 year and <10 years	<.0001	<.0001	1.000	<.0001	0.5907	0.0699	0.2018	
TSLE is ≥ 2.5 years and <5 years	0.0596	-0.0926	-0.0548	0.1208	-0.0241	0.0769	-0.0359	
TSLE is ≥ 0 years and <2.5 years	0.1537	0.0265	0.1897	1.000	0.5644	0.0655	0.3902	
	0.0617	-0.1883	0.2003	0.1208	0.0034	0.0046	-0.0055	
	0.1394	<.0001	<.0001	0.0037	1.000	0.9120	0.8945	
	-0.0150	0.0578	0.0225	-0.0241	0.0034	-0.1037	-0.1591	
	0.7193	0.1664	0.5907	0.5644	0.9349	1.000	0.0001	
	0.0295	-0.0036	0.0757	0.0769	0.0046	-0.1037	-0.1209	
	0.4806	0.9317	0.0699	0.0655	0.9120	0.0129	1.000	
	0.0129	0.0049	-0.0533	-0.0359	-0.0055	-0.1591	-0.1209	
	0.7581	0.9066	0.2018	0.3902	0.8945	0.0001	0.0037	
							1.000	

Table 7: Final Regression Model—On-Site Badge Exposure Only (Estimated Missed Exposure and Exposure from Off-Site Sources Excluded) Two Year Lag								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Confidence Limits	
						(10 mSv) 1.08	1.01	1.16
Badge Exposure - Lagged 2 Years (1 mSv)	1	0.0077	0.0035	4.847	0.0277	(1 mSv) 1.01	1.00	1.02
Gender	1	-1.1939	0.6112	3.816	0.0508	0.30	0.09	1.00
Radiation Worker (1=Yes, 0=No)	1	-0.7259	0.2625	7.645	0.0057	0.48	0.29	0.81
Solvent Duration Exposure - Lagged 2 Years	1	0.0323	0.0115	7.861	0.0051	1.03	1.01	1.06

Exposure Variable (1 mSv)	DF	Parameter Estimate	Standard Error	Odds Ratio	95% Confidence Limits	LR Test Chi-Sq	Pr > Chi-Sq
Occupational Bone Marrow Dose No Lag	1	0.0057	0.0041	1.01	0.99 1.01	1.820	0.18
Occupational Bone Marrow Dose Lagged 2 Years	1	0.0059	0.0041	1.01	0.99 1.01	1.905	0.17
Occupational Bone Marrow Lagged 5 Years	1	0.0060	0.0043	1.01	0.99 1.01	1.798	0.18
Occupational Bone Marrow Dose Lagged 7 Years	1	0.0059	0.0044	1.01	0.99 1.02	1.703	0.19

Table 9: Occupational Bone Marrow Dose Variable Combined with Work-Related Medical X-Ray Dose with Zero, Two, Five, and Seven Year Lags								
Exposure Variable (1 mSv)	Parameter DF	Standard Estimate	Standard Error	Odds Ratio	95%		LR Test Chi-Sq	Pr > Chi-Sq
					Confidence Limits			
Occupational Bone Marrow Dose + Medical X-Rays—Lagged No Lag	1	0.0061	0.0039	1.01	0.99	1.01	2.214	0.14
Occupational Bone Marrow Dose + Medical X-Rays—Lagged 2 Years	1	0.0063	0.0040	1.01	0.99	1.01	2.348	0.13
Occupational Bone Marrow Dose + Medical X-Rays—Lagged 5 Years	1	0.0063	0.0041	1.01	0.99	1.01	2.159	0.14
Occupational Bone Marrow Dose + Medical X-Rays—Lagged 7 Years	1	0.0061	0.0042	1.01	0.99	1.02	1.971	0.16

Model	DF	-2 LOG L With Covariates	-2 LOG L With Covariates Differences	Critical Value-Chi- Sq (0.05)
A) Full model with 2-way, and main effects	9	341.49		
B) Reduced model 2-way exposure interactions and main effects	8	341.706	B-A = 0.210 1 df	3.84
C) Reduced model—main effects only	7	342.99	C-B = 1.23 1 df	3.84

Table 11: Model A—Full model with 2-Way, Interactions and Main Effects—Occupational Bone Marrow Dose Only—Two Year Lag								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Odds Ratio	95% Confidence Limits	
On & Offsite Occupational Dose Lagged 2 Years (1 mSv)	1	0.0148	0.0065	5.123	0.0236	1.02	1.00	1.03
Gender (1=Female, 0=Male)	1	-1.171	0.6186	3.585	0.0583	0.31	0.09	1.04
Radiation Worker (1=Yes, 0=No) Lagged 2 yrs	1	-0.7413	0.3559	4.340	0.0372	0.47	0.24	0.96
Solvent Duration Exposed - Lagged 2 Years	1	0.0436	0.0150	8.457	0.0036	1.05	1.01	1.08
TSLE is ≥ 5 year and <10 years	1	-0.1644	0.3619	0.2063	0.6497	0.85	0.42	1.73
TSLE is ≥ 2.5 years and <5 years	1	0.6333	0.4078	2.412	0.1204	1.88	0.85	4.19
TSLE is ≥ 0 years and <2.5 years	1	-0.5699	0.4152	1.884	0.1699	0.57	0.25	1.28
On & Offsite Occupational Dose * Solvent Duration Exposure	1	-0.0004	0.0005	0.6404	0.4235	1.000	0.99	1.00
Radiation Worker * Solvent Duration Exposed	1	-0.0122	0.0264	0.2124	0.6449	0.99	0.94	1.04

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Odds Ratio	95% Confidence Limits	
On & Offsite Occupational Dose Lagged 2 Years (1 mSv)	1	0.0158	0.0062	6.538	0.0106	1.02	1.00	1.03
Gender (1=Female, 0=Male)	1	-1.195	0.6159	3.764	0.0524	0.30	0.09	1.01
Radiation Worker (1=Yes, 0=No) Lagged 2 yrs	1	-0.8493	0.2731	9.675	0.0019	0.43	0.25	0.73
Solvent Duration Exposed - Lagged 2 Years	1	0.0398	0.0125	10.10	0.0015	1.04	1.02	1.07
TSLE is ≥ 5 year and <10 years	1	-0.1673	0.3620	0.2136	0.6440	0.85	0.47	1.72
TSLE is ≥ 2.5 years and <5 years	1	0.6338	0.4075	2.419	0.1199	1.89	0.85	4.19
TSLE is ≥ 0 years and <2.5 years	1	-0.5635	0.4152	1.842	0.1747	0.57	0.25	1.28
On & Offsite Occupational Dose * Solvent Duration Exposure	1	-0.0005	0.0005	1.174	0.2785	0.99	0.99	1.00

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Odds Ratio	95% Confidence Limits	
On & Offsite Occupational Dose Lagged 2 Years (1 mSv)	1	0.0112	0.0048	5.517	0.0188	1.01	1.00	1.02
Gender (1=Female, 0=Male)	1	-1.234	0.6140	4.042	0.0444	0.29	0.09	0.97
Radiation Worker (1=Yes, 0=No) Lagged 2 yrs	1	-0.8289	0.2724	9.261	0.0023	0.44	0.26	0.74
Solvent Duration Exposed - Lagged 2 Years	1	0.0348	0.0117	8.898	0.0029	1.04	1.01	1.06
TSLE is ≥ 5 year and <10 years	1	-0.1670	0.3606	0.215	0.6433	0.85	0.42	1.72
TSLE is ≥ 2.5 years and <5 years	1	0.6650	0.4073	2.665	0.1026	1.94	0.88	4.32
TSLE is ≥ 0 years and <2.5 years	1	-0.4937	0.4113	1.440	0.2301	0.61	0.27	1.37

Table 14: Model Fit Statistics—Occupational Bone Marrow Dose Combined with Bone Marrow Dose from Medical X-Ray Examinations				
Model	DF	-2 LOG L With Covariates	-2 LOG L With Covariates Differences	Critical Value-Chi-Sq (0.05)
A) Full model with 2-way, 3-way and main effects	12	343.94		
B) Reduced model 2-way exposure interactions and main effects	10	346.50	B-A = 2.56 2 df	5.99
C) Reduced model—main effects only	7	347.75	C-B = 1.25 3 df	7.81

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Odds Ratio	95% Confidence Limits	
On & Offsite Occ + Med X-Ray Dose - Lag 2 Years (1 mSv)	1	-0.0528	0.0679	0.6045	0.4369	0.95	0.83	1.08
Gender (1=Female, 0=Male)	1	-2.081	1.089	3.654	0.0559	0.13	0.02	1.05
Radiation Worker (1=Yes, 0=No)	1	-0.8946	0.4435	4.069	0.0437	0.41	0.17	0.98
Solvent Duration Exposed - Lagged 2 Years	1	0.0024	0.0323	0.0054	0.9413	1.00	0.94	1.07
TSLE is ≥ 5 year and <10 years	1	-0.3091	0.3875	0.6364	0.4250	0.73	0.34	1.57
TSLE is ≥ 2.5 years and <5 years	1	-0.0036	0.4464	0.0001	0.9935	0.99	0.425	2.39
TSLE is ≥ 0 years and <2.5 years	1	-0.2003	0.4219	0.2255	0.6349	0.82	0.36	1.87
On & Offsite Occ + Med X-Ray Dose * Solv Dur Exp	1	0.0069	0.0050	1.959	0.1616	1.01	0.99	1.02
Rad Worker * Solv Dur Exp	1	0.0258	0.0404	0.4062	0.5239	1.03	0.95	1.11
On & Offsite Occ + Medical X-Ray Dose * Rad Worker- Lag 2 yrs	1	0.0657	0.0686	0.9160	0.3385	1.07	0.93	1.22
On & Offsite Occ + Medical X-Ray Dose * Gender	1	0.2343	0.1901	1.519	0.2178	1.26	0.87	1.84
On & Offsite Occ + Med X-Ray Dose * Rad Worker-Lag 2 yrs * Solv Dur Exp	1	-0.0072	0.0050	2.085	0.1488	0.99	0.98	1.00

Table 16: Model B—Reduced Model with 2-Way Exposure Interactions and Main Effects—Occupational Bone Marrow Dose Combined with Work-Related Medical X-Ray Dose—Two Year Lag								
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Odds Ratio	95% Confidence Limits	
On & Offsite Occ + Med X-Ray Dose - Lag 2 Years (1 mSv)	1	0.0130	0.0516	0.0636	0.8009	1.01	0.92	1.12
Gender (1=Female, 0=Male)	1	-1.841	1.069	2.973	0.0850	0.16	0.02	1.29
Radiation Worker (1=Yes, 0=No)	1	-0.7462	0.3682	4.108	0.0427	0.47	0.23	0.98
Solvent Duration Exposed - Lagged 2 Years	1	0.0367	0.0147	6.236	0.0125	1.04	1.01	1.07
TSLE is ≥ 5 year and <10 years	1	-0.3269	0.3879	0.7103	0.3994	0.72	0.34	1.54
TSLE is ≥ 2.5 years and <5 years	1	-0.0242	0.4454	0.0029	0.9567	0.98	0.41	2.34
TSLE is ≥ 0 years and <2.5 years	1	-0.2322	0.4223	0.3024	0.5824	0.79	0.35	1.81
On & Offsite Occ Dose + Work-Related Medical X-Ray Dose * Radiation Worker-Lagged 2 yrs	1	0.0001	0.0526	0.0001	0.9983	1.00	0.90	1.11
On & Offsite Occ Dose + Work-Related Medical X-Ray Dose * Gender	1	0.1592	0.1812	0.7713	0.3798	1.17	0.82	1.67
On & Offsite Occ Dose + Work-Related Medical X-Ray Dose * Solvent Duration Exposure	1	-0.0003	0.0005	0.4334	0.5103	1.00	0.99	1.00

Table 17: Model C Main Effects Only— Occupational Bone Marrow Dose Combined with Work-Related Medical X-Ray BMD- Two Year Lag								
Variable	DF	Parameter Estimate	Standard Error	Chi-Sq	Pr > ChiSq	Odds Ratio	95% Confidence Limits	
On & Offsite Occ + Med X-Ray						(10 mSv) 1.11	1.02	1.22
Dose - Lag 2 Years	1	0.0107	0.0046	5.391	0.0202	(1 mSv) 1.01	1.00	1.02
Gender	1	-1.206	0.6119	3.884	0.0487	0.30	0.09	0.99
Radiation Worker (1=Yes, 0=No)	1	-0.7332	0.2692	7.418	0.0065	0.48	0.28	0.81
Solvent Duration Exp - Lagged 2 Years	1	0.0315	0.0117	7.275	0.0070	1.03	1.01	1.06
TSLE is ≥ 5 year and <10 years	1	-0.3057	0.3859	0.627	0.4282	0.74	0.35	1.57
TSLE is ≥ 2.5 years and <5 years	1	-0.0510	0.4454	0.013	0.9088	0.95	0.40	2.28
TSLE is ≥ 0 years and <2.5 years	1	-0.1707	0.4140	0.170	0.6801	0.84	0.37	1.90

Table 18: Final Regression Model—On-Site BMD Only + Medical BMD—Two Year Lag

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Confidence Limits	
On Site BMD + Med BMD Cum Dose - Lagged 2 Years	1	0.0109	0.0046	5.603	0.0179	(10 mSv) 1.12 (1 mSv) 1.01	1.02	1.22
Gender	1	-1.198	0.6110	3.844	0.0499	0.30	0.09	1.00
Radiation Worker (1=Yes, 0=No)	1	-0.7559	0.2654	8.109	0.0044	0.47	0.28	0.79
Solvent Duration Exposure - Lagged 2 Years	1	0.0312	0.0115	7.370	0.0066	1.03	1.01	1.06

Table 19: Amount of Collective Cumulative Bone Marrow Dose and Whole Body Exposure Received from Estimated Missed Exposure, Onsite, and Offsite Sources for the 201 Radiation Monitored Cases and Controls

Source	Collective Bone Marrow Dose (person-mSv)	Collective Whole Body Exposure (person-mSv)	Difference (person-mSv)
Onsite Only	3,429.50	4,658.29	1,228.79
Estimated Missed	60.92	87.59	26.67
Offsite Only	7.63	10.92	3.29
Total	3,498.05	4,756.80	1,258.75

Table 20: Formula for the Computation of Odds Ratio and 95% Confidence Intervals for the Radiation Exposure * Time Since Last Exposed (TSLE) Category

The relative risk at (1 mSv and 10 mSv) exposure levels and TSLE category of interest

$$e^{\hat{\beta}_1(f_1 - f_0) + \hat{\beta}_3 X(f_1 - f_0)}$$

Confidence Interval on Relative Risk at exposure f_1 and TSLE category of interest

$$e^{\text{contrast} \pm 1.96 \sqrt{\text{var}(\hat{\beta}_1(f_1 - f_0)^2 + \text{var}(\hat{\beta}_3)[X(f_1 - f_0)]^2 + 2 * \text{cov}(\hat{\beta}_1, \hat{\beta}_3) X(f_1 - f_0)^2}}$$

$\hat{\beta}_1$ = The estimated dose parameter

$\hat{\beta}_3$ = Estimated dose * TSLE category interaction parameter

$\text{Cov}(\hat{\beta}_1, \hat{\beta}_3)$ = Covariance of the dose parameter and the dose * TSLE category interaction parameter

f_1 = Exposure level of interest (eg. 1 mSv or 10 mSv)

f_0 = Comparison exposure level (eg. 0 mSv)

X = Dummy variable corresponding to the TSLE category ($X=1$)

**Table 21: Variance Covariance Matrix—Categories (≥ 10 yrs TSLE;
 ≥ 5 - <10 yrs TSLE; ≥ 2.5 - <5 yrs TSLE;
 ≥ 0 - <2.5 yrs TSLE)**

Rad Exposure (1 mSv)	Rad Exposure * ≥ 10 years TSLE	Rad Exposure * \geq 5 and <10 years TSLE	Rad Exposure * ≥ 2.5 and <5 years TSLE	Rad Exposure* ≥ 0 and <2.5 years TSLE
Parameter Estimates	0.00709	-0.04571	0.04330	0.00203
Rad Exposure * ≥ 10 years TSLE	(Variance) 0.000015657	(Variance Covariance) -0.000011	(Variance Covariance) -0.000012	(Variance Covariance) -0.000013
Rad Exposure * ≥ 5 and <10 years TSLE	-0.000011	(Variance) 0.001745	0.000030	0.000010566
Rad Exposure * ≥ 2.5 and <5 years TSLE	-0.000012	0.000030	(Variance) 0.000470	0.000017158
Rad Exposure * ≥ 0 and <2.5 years TSLE	-0.000013	0.000011	0.000017	(Variance) 0.000075935

Table 22: Variance Covariance Matrix—Categories ($\geq 0 - \leq 3$ yrs TSLE; $>3 - \leq 7$ yrs TSLE; > 7 yrs TSLE)

Rad Exposure (1 mSv)	Rad Exposure * > 7 years TSLE	Rad Exposure * ≥ 0 and <3 years TSLE	Rad Exposure * ≥ 3 and ≤ 7 years TSLE
Parameter Estimates	0.00620	0.0004484	0.04301
Rad Exposure * > 7 years TSLE	(Variance) 0.000015	(Variance Covariance) -0.00001313	(Variance Covariance) -0.000011
Rad Exposure * ≥ 0 and ≤ 3 years TSLE	-0.00001313	0.000071963	0.000017
Rad Exposure * > 3 and ≤ 7 years TSLE	-0.000011	0.000016993	0.000308

Table 23: Variance Covariance Matrix—Categories (≥ 10 yrs. TSLE; ≥ 5 - <10 yrs TSLE; ≥ 2.5 - <5 yrs TSLE; ≥ 0 - <2.5 yrs TSLE)

Rad Exposure (1 mSv)	Rad Exposure * ≥ 10 years TSLE	Rad Exposure * ≥ 5 and <10 years TSLE	Rad Exposure * ≥ 2.5 and <5 years TSLE	Rad Exposure * ≥ 0 and <2.5 years TSLE
Parameter Estimates	0.00913	0.00991	0.00071	0.00153
Rad Exposure* ≥ 10 years TSLE	(Variance) 0.000034	(Variance Covariance) -0.000030	(Variance Covariance) -0.000031	(Variance Covariance) -0.000031
Rad Exposure * ≥ 5 and <10 years TSLE	-0.000030	(Variance) 0.000204	0.000031	0.000028
Rad Exposure * ≥ 2.5 and <5 years TSLE	-0.000031	0.000031	(Variance) 0.000159	0.000027
Rad Exposure * ≥ 0 and <2.5 years TSLE	-0.000031	0.000028	0.000027	(Variance) 0.000115

Table 24: Variance Covariance Matrix—Categories (>7 yrs TSLE; $\geq 0 - \leq 3$ yrs TSLE; >3 - ≤ 7 yrs TSLE)			
Rad Exposure (1 mSv)	Rad Exposure * > 7 years TSLE	Rad Exposure * ≥ 0 and <3 years TSLE	Rad Exposure * ≥ 3 and ≤ 7 years TSLE
Parameter Estimates	0.01113	-0.00139	0.00280
Rad Exposure * > 7 years TSLE	(Variance) 0.000030	(Variance Covariance) -0.0000264	(Variance Covariance) -0.0000259
Rad Exposure * ≥ 0 and ≤ 3 years TSLE	-0.0000264	(Variance) 0.000111	0.000024
Rad Exposure * > 3 and ≤ 7 years TSLE	-0.0000259	0.000024	(Variance) 0.000155

Table 25: Model Fit Statistics —Badge Exposure with TSLE as a Continuous Variable				
Model	DF	-2 LOG L With Covariates	-2 LOG L With Covariates Differences	Critical Value-Chi-Sq (0.05)
A) Full model with 2-way, and main effects	12	347.32		
B) Reduced model 2-way exposure interactions and main effects	7	348.32	B-A = 1.01 5 df	11.07
C) Reduced model—main effects only	5	349.20	C-B = 0.88 2 df	5.99

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Odds Ratio	95% Confidence Limits	
On/Offsite Badge Cum Exp – Lag 2 Years	1	0.0069	0.0080	0.7413	0.3892	1.01	0.99	1.02
Gender	1	-1.470	1.086	1.833	0.1758	0.23	0.03	1.93
Radiation Worker Lagged 2 yrs	1	-0.3699	0.5258	0.4951	0.4817	0.69	0.25	1.94
Solv Dur Exp - Lag 2 Years	1	0.0300	0.0222	1.827	0.1765	1.03	0.99	1.08
TSLE	1	-0.0016	0.0136	0.0132	0.9086	0.99	0.97	1.03
On/Off Badge lag2*TSLE	1	0.0002	0.0005	0.1484	0.7001	1.00	0.99	1.00
On/Off Badge lag 2 * Solv_Lag2	1	-0.0002	0.0008	0.0801	0.7772	1.00	0.99	1.00
On/Off Badge lag2*Solv_lag2*TSLE	1	4.9579E-7	0.00006	0.0001	0.9942	1.00	1.00	1.00
Rad worker lag2*Solv_lag2	1	-0.0117	0.0266	0.1933	0.6602	0.99	0.94	1.04
Rad worker lag2*TSLE	1	-0.0202	0.0285	0.5068	0.4765	0.98	0.93	1.04
Gender* TSLE	1	0.0190	0.0468	0.1643	0.6853	1.02	0.93	1.12
Solv_lag2*TSLE	1	0.0007	0.0013	0.3063	0.5800	1.00	0.99	1.00

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Odds Ratio	95% Confidence Limits	
On/Off Badge								
Lag 2 Years	1	0.0100	0.0068	2.177	0.1401	1.01	0.99	1.02
Gender	1	-1.159	0.6129	3.577	0.0586	0.31	0.09	1.04
Rad Worker								
Lag 2 yrs.	1	-0.7436	0.2634	7.967	0.0048	0.48	0.28	0.80
Solv Dur Exp								
Lag 2 Years	1	0.0358	0.0127	8.014	0.0046	1.04	1.01	1.06
TSLE	1	-0.0012	0.0120	0.0102	0.9196	0.99	0.98	1.02
On/Off Badge								
Lag2*Solv_lag2	1	-0.0003	0.0004	0.8450	0.3580	1.00	0.99	1.00
On/Off Badge								
Lag2*TSLE	1	0.00003	0.0004	0.0047	0.9451	1.00	0.99	1.00

Table 28: Mode C—Main Effects—Badge Exposure—Two Year Lag—TSLE Included as a Continuous Variable

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Confidence Limits	
Badge Cum Exposure - Lagged 2 Years	1	0.0076	0.0035	4.769	0.0290	1.01	1.00	1.02
Gender	1	-1.193	0.6112	3.808	0.0510	0.30	0.09	1.01
Radiation Worker flag	1	-0.72819	0.2631	7.658	0.0057	0.48	0.29	0.81
Solvent Duration Exp – Lagged 2 Years	1	0.0318	0.0119	7.150	0.0075	1.03	1.01	1.06
TSLE	1	-0.0021	0.0119	0.0317	0.8587	0.99	0.98	1.02

Table 29: Time Windows of Exposure Analysis

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Confidence Limits	
Gender	1	-1.1940	0.6105	3.825	0.0505	0.30	0.09	1.00
Rad_Worker	1	-0.7757	0.2694	8.291	0.0040	0.46	0.27	0.78
Solvent Exposure 0 < 2.5 yrs. Window	1	-0.1849	0.1941	0.9077	0.3407	0.83	0.57	1.22
2.5<5 yrs. Window	1	0.0208	0.0438	0.2253	0.6350	1.02	0.94	1.11
5<10 yrs. Window	1	0.03529	0.0161	4.758	0.0292	1.04	1.00	1.07
≥ 10 yrs. Window	1	0.0064	0.0038	2.902	0.0885	1.01	0.99	1.01

Table 30: Description of All Radiation Dose Metrics Used in the Regression Analysis in Order of Appearance or Reference in Report

Radiation dose metric label	Table	Page	Radiation dose included in the metric
Occupational Badge Exposure 0,2,5,7, Yr Lags	4.5.1	33	Cumulative onsite and off site badge exposure and missed exposure combined: 0,2,5, and 7 year lag periods
Occupational Badge Exposure Lagged 2 years	4.5.2.A., 4.5.2.B. & 4.5.3	34, 35, 37	Cumulative onsite and offsite occupational badge exposure and Missed Exposure combined with 2 yr lag
On & Offsite & Missed Badge Cumulative Exposure - Lagged 2 Years	Appendix K Tables 3, 4, 5,6	148-151	Cumulative onsite and offsite badge exposure and Missed Exposure combined with a 2 year lag
Onsite Badge Exposure - Lagged 2 Years	Appendix KTable 7	152	Cumulative onsite badge exposure ONLY (Missed and Offsite are excluded)-2 yr lag
Occupational Bone Marrow Cum Dose 0, 2, 5, 7, yr lags	Appendix K Table 8	153	Cumulative onsite and off site Occupational badge exposure & missed exposure combined converted to BMD—0,2,5,7 year lag periods
Occupational Cumulative BMD + Medical X-Ray Dose Lagged 0, 2, 5, 7 yr	Appendix K Table 9	154	Cumulative onsite and off site Occupational badge exposure & missed exposure combined and converted to BMD + Med X-Ray BMD—0,2,5,7, year lag periods
Occupational Cumulative Bone Marrow Dose Only-2 yr lag	Appendix K Table 10,11,12,13	155-158	Cumulative onsite and off site occupational badge exposure and missed exposure combined & converted to BMD—2 year lag period
Occupational Cumulative BMD + Medical X-Ray Dose	Appendix K Table 14,15,16,17	159-162	Cumulative onsite and off site badge exposure & missed exposure combined and converted to BMD + Medical X-Ray BMD Dose—lagged 2 years

Table 30: Description of All Radiation Dose Metrics Used in the Regression Analysis in Order of Appearance or Reference in Report

Radiation dose metric label	Table	Page	Radiation dose included in the metric
Onsite BMD + Med BMD Cum Dose Lag 2 yrs	Appendix K Table 18	163	Cumulative onsite badge exposure converted to BMD (Missed Exposure and offsite exposure are excluded) + Medical X-Ray BMD—2 year lag period
Cum Rad Badge Exposure	Appendix K Table 21-22	165-166	Cumulative Onsite and Off site occupational badge exposure combined—No lag—(No Missed Exposure)
Cum Rad Badge Exposure	Appendix K Table 23-24	167-168	Cumulative Onsite and Off site occupational badge exposure combined converted to BMD + Medical X-Ray BMD—No lag—(No Missed Exposure)
Occupational Bone Marrow Cum Dose Lagged 2 Years	4.5.4.1.	38	BMD converted from onsite and offsite badge exposure and missed exposure combined—Lagged 2 Years
Occupational Cumulative BMD + Medical X-Ray BMD Lagged 2 yrs.	4.5.4.2	39	Onsite and off site cumulative badge exposure and missed exposure converted to BMD + Work-Related Medical X-Rays given at PNS—lagged 2 years
Cum Rad Exposure	4.5.5.A.,B,C, & D	40-42	Cumulative Onsite and Off site badge exposure combined (No Missed Exposure Included)—2 yr. lag
Occupational Cumulative BMD + Medical X-Ray Dose Lagged 2 yrs.	4.5.6.A. & B	43-44	Onsite and off site cumulative badge exposure converted to BMD + Work-Related Medical X-Rays given at PNS (No Missed Exposure Included)—2 year lag period
Badge Exposure with TSLE as a Continuous Variable	Appendix K Table 25	169	Onsite and offsite cumulative badge exposure and missed exposure—lagged 2 years
On/Offsite Badge Cum Exp – Lag 2 Years	Appendix K Table 26	170	Onsite and offsite cumulative badge exposure and missed exposure—lagged 2 years

Table 30: Description of All Radiation Dose Metrics Used in the Regression Analysis in Order of Appearance or Reference in Report

Radiation dose metric label	Table	Page	Radiation dose included in the metric
Badge Cum Exposure - Lagged 2 Years	Appendix K Table 27	171	Onsite and offsite cumulative badge exposure and missed exposure-lagged 2 years
Badge Cum Exposure - Lagged 2 Years	Appendix K Table 28	172	Onsite and offsite cumulative badge exposure and missed exposure-lagged 2 years
On & off site Badge – Win 0-2.5 yr			
On & off site badge - Win 2.5-5 yr			
On & off site badge – Win 5-10 yr			
On & off badge – Win >10 yr	Appendix K Table 29	172	For each exposure window—Onsite and offsite cumulative badge exposure no missed exposure no lag
Radiation Dose Category			
1 - < 1 mSv			
10 - <50 mSv	Appendix K		For each dose category—Onsite and offsite cumulative badge and missed exposure 2 yr lag
>50 mSv	Table 37	182	

Table 31: Dose Distribution Radiation Monitored Cases

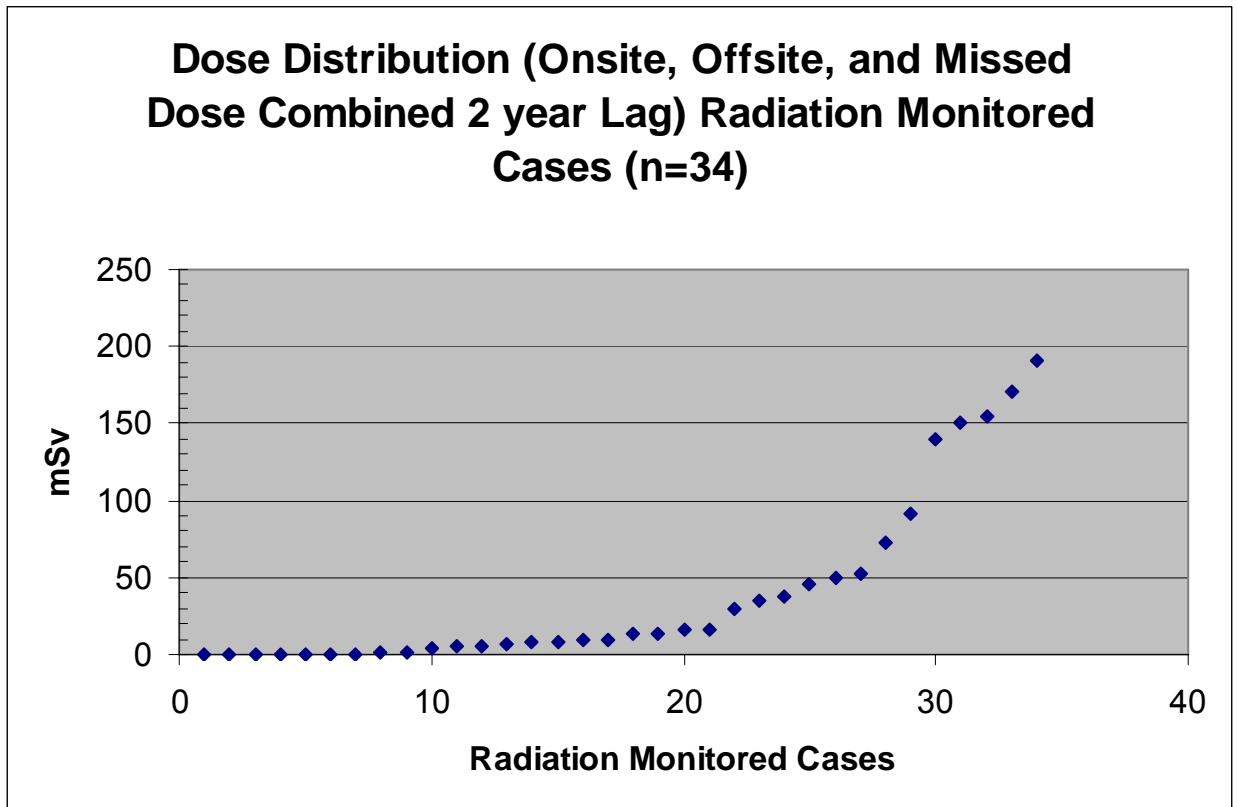


Table 32: Dose Distribution Radiation Monitored Controls

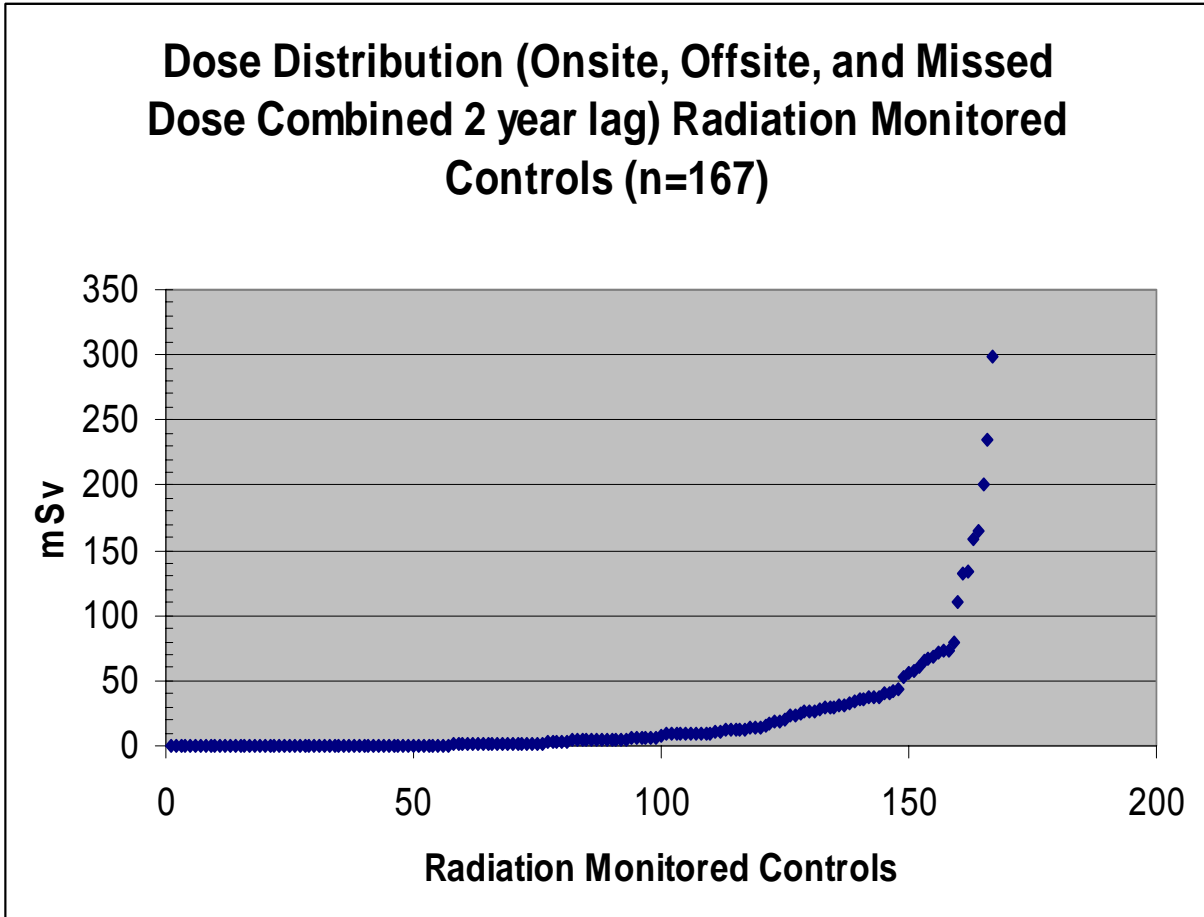


Table 33: Distribution of Solvent Duration (yrs) Radiation Monitored Cases

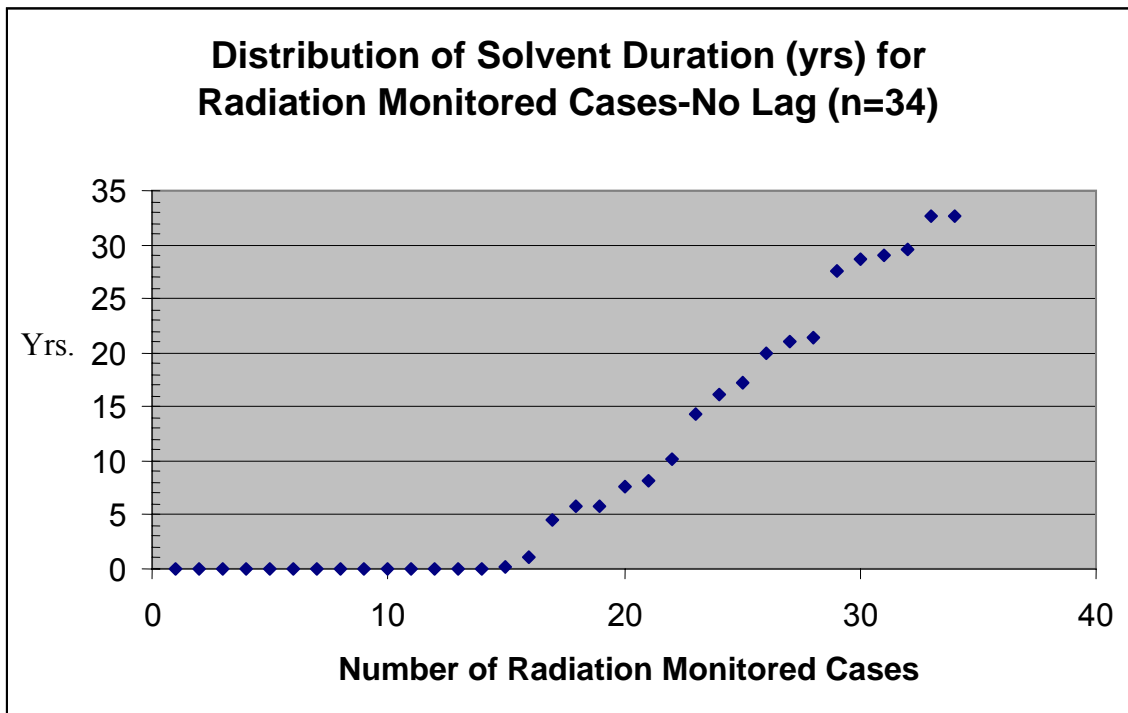


Table 34: Distribution of Solvent Duration (yrs) Non-Radiation Monitored Cases

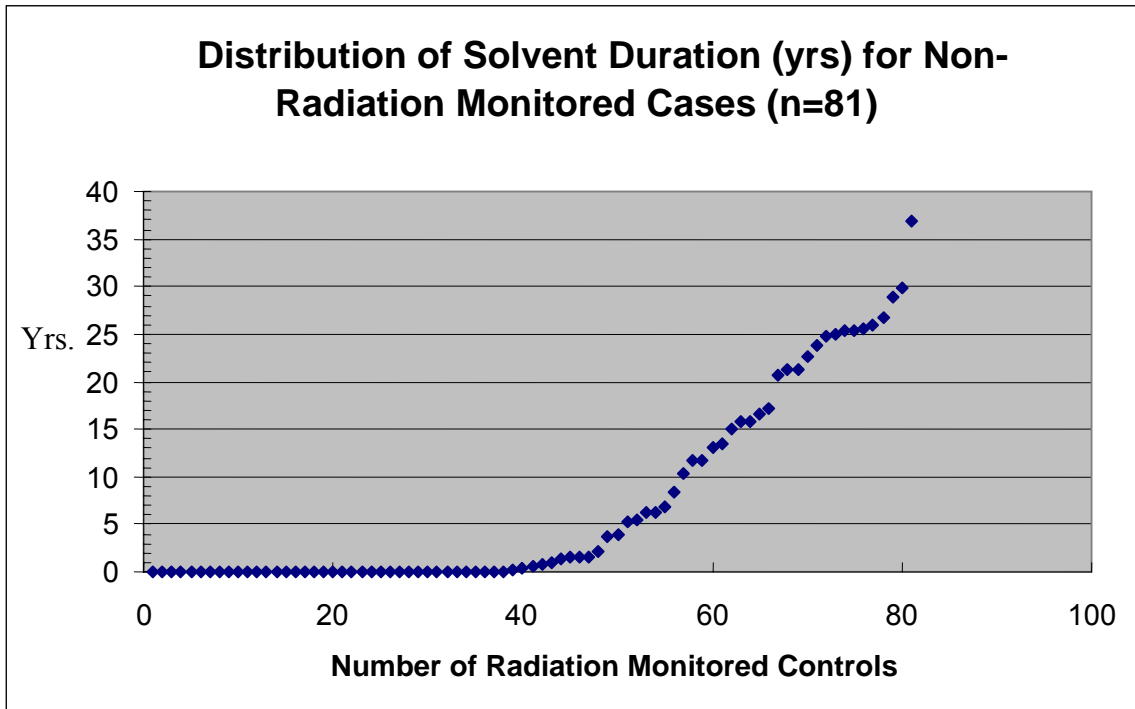


Table 35: Distribution of Solvent Duration (yrs) Radiation Monitored Controls

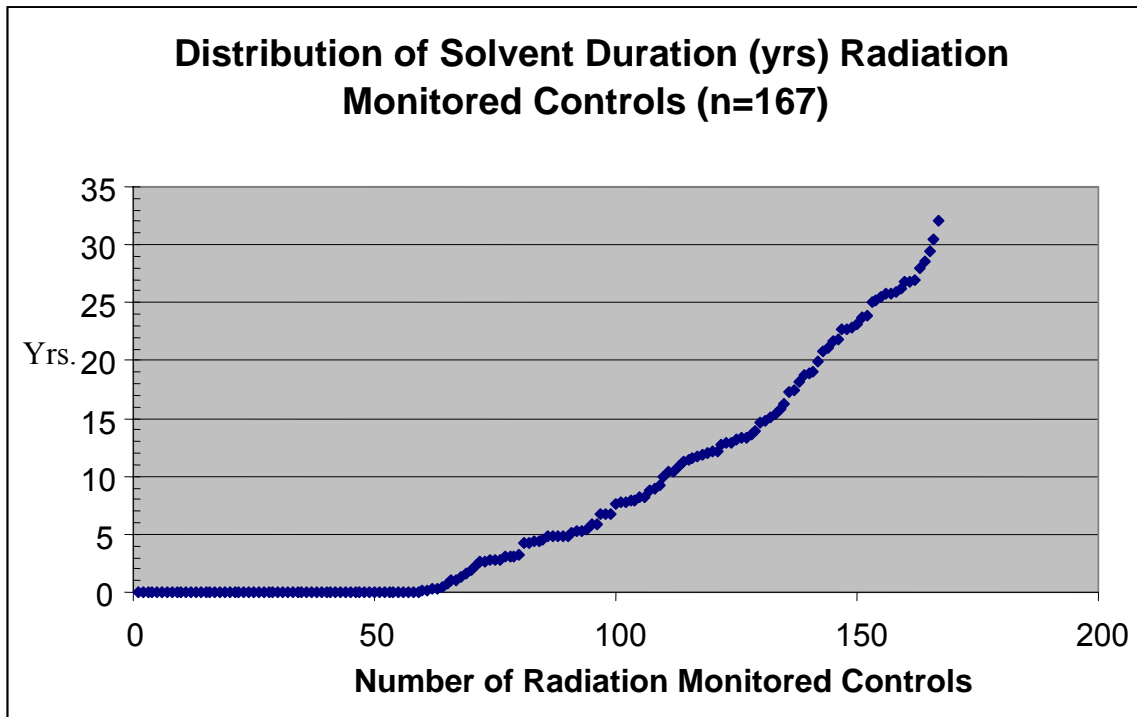


Table 36: Distribution of Solvent Duration (yrs) Non-Radiation Monitored Controls

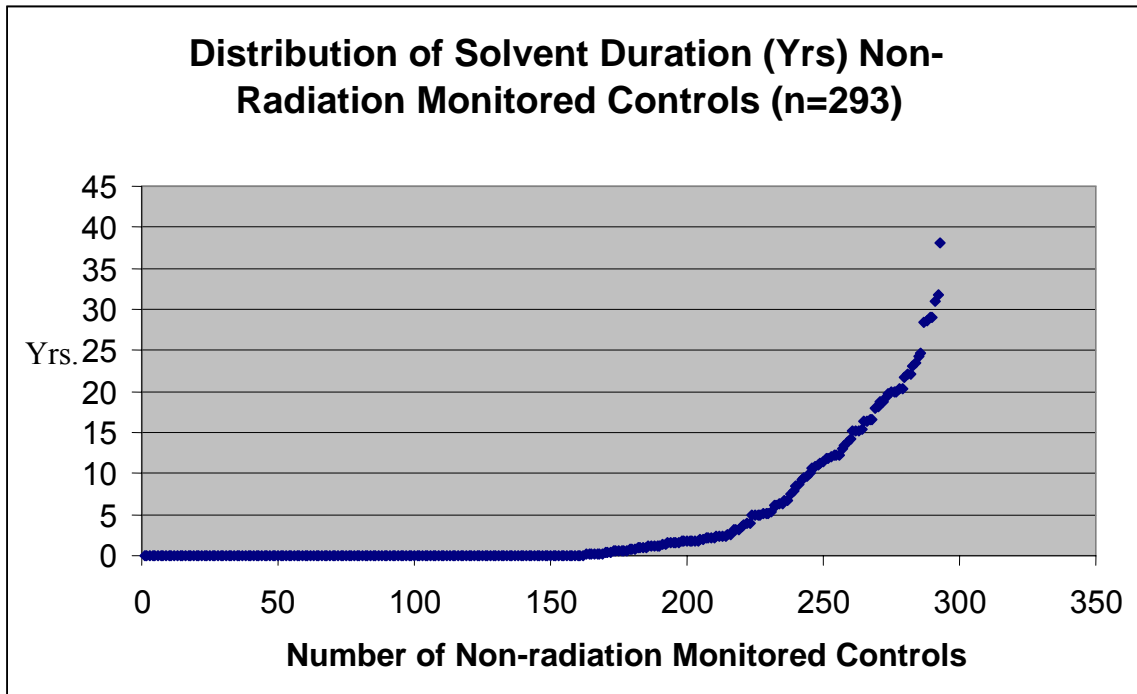


Table 37: OR by Dose Category Onsite, Offsite, and Missed Badge Dose Lagged Two years (n=201 Radiation Monitored Workers)								
Dose Category	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Odds Ratio	95% Confidence Limits	
1<10 mSv	1	0.464	0.703	0.436	0.509	1.59	0.40	6.31
10<50 mSv	1	0.648	0.646	1.005	0.316	1.91	0.54	6.79
≥50 mSv	1	1.557	0.775	4.043	0.044	4.75	1.04	21.66

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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