Revised Research Protocol

for

A Study of Cancer among United States Firefighters

March 20, 2011
(Online Version)

Industrywide Studies Branch (IWSB)
Division of Surveillance, Hazard Evaluation and Field Studies (DSHEFS)
National Institute for Occupational Safety and Health (NIOSH)

Foreword

This project was originally submitted as an intramural research project to the National Occupational Research Agenda (NORA) program. The project proposal was reviewed and strongly recommended for funding by both internal NIOSH and external peer reviewers. The NIOSH Office of the Director has authorized that the project proceed and that a protocol be submitted to the NIOSH Human Subjects Review Board (HSRB) for approval. The text of the original NORA study proposal is contained in the reformatted protocol to meet HSRB protocol format requirements. Information required for the initial proposal but not pertinent to this protocol (i.e., detailed study budget, and the Curriculum Vitae of project collaborators) have been removed.

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**Available upon request*

List of Acronyms and Abbreviations

CDC	Centers for Disease Control and Prevention
CI	confidence interval
CLL	chronic lymphocytic leukemia
CO	carbon monoxide
COD	cause of death
CVD	cardiovascular disease
HSRB	Human Subjects Review Board
HHS	U.S. Department of Health and Human Services
HWE	Healthy worker effect
IAFC	International Association of Fire Chiefs
IAFF	International Association of Firefighters
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IRS	Internal Revenue Service
JEM	job-exposure matrix
NCHS	National Center for Health Statistics
NDI	National Death Index
NHL	non-Hodgkin's lymphoma
NIOSH	National Institute for Occupational Safety and Health
PAH	polycyclic aromatic hydrocarbons
PPE	Personal Protective Equipment
RR	relative risk
SE	standard error
SSA-DMF	Social Security Administration Death Master File
SMR	standardized mortality ratio
SIR	standardized incidence ratio
SRR	standardized rate ratio
SCBA	Self Contained Breathing Apparatus
U.S.	United States

PROJECT OVERVIEW

Title
A Study of Cancer among United States Firefighters

Protocol Summary
The primary objective of the project is to clarify the relationship between firefighter occupational exposures and cancer. The project will improve upon previously published firefighter studies by 1) significantly increasing the study cohort size and person-years at risk, and 2) using a more detailed exposure surrogate metric in both the mortality and incidence analyses than are found in most previous studies. These improvements will increase the precision of disease risk estimates.

The objectives of the study are 1) to establish a pooled cohort of career firefighters from both suburban and large city fire departments to study the relationship between firefighter occupational exposures and cancer, 2) to conduct a retrospective mortality study among the cohort of career firefighters, 3) to determine the incidence of cancer among the firefighter cohort members, 4) to examine the relationship between occupational exposures and cause-specific mortality and cancer incidence among firefighters.

Study results and recommendations will be translated and communicated through collaboration with the International Association of Firefighters (IAFF), the International Association of Fire Chiefs (IAFC), the Firefighter Cancer Support Network, labor and management from each participating fire department, and other firefighter organizations (e.g., the United States Fire Administration, National Volunteer Fire Council, and the National Fire Protection Association). All manuscripts will be submitted to peer-reviewed scientific journals.

The time frame for the project is 2010 – 2013.

External Collaborators

This research requires a multidisciplinary approach, drawing NIOSH expertise from DSHEFS (epidemiology, statistics, exposure-assessment, computer programming, and data management). NIOSH researchers will collaborate with the following external researchers with expertise in epidemiology and industrial hygiene who have conducted occupational research studies of firefighters. None of the external collaborators will have access to identified study data. *Epidemiology:* James Beaumont, Ph.D., University of California, Dalsu Baris, M.D., Ph.D., National Cancer Institute, Shelia Hoar-Zahm, Sc.D. National Cancer Institute, and Paul Demers, Ph.D. University of British Columbia. Drs. Beaumont, Barris, and Zahm will have access to identified information. They will provide review and consultation about the epidemiological methods and analyses. Dr. Demers will not have access to identified data and will only provide consultation and review of the epidemiological methods and analyses.

Exposure Assessment/Industrial Hygiene: Claire C., Austin, Ph.D. Environment Canada, Air Quality Research Division, and John T. Jankovic, M.S., Oak Ridge National Laboratory. These individuals will not have access to identified information and will only provide review and consultation about exposure assessment and Job Exposure Matrix (JEM) development.

Funding Sources
Funding for this study is from NIOSH funds including funding awarded under the National Occupational Research Agenda (NORA).

INTRODUCTION

Literature Review/Current State of Knowledge

Inhalational exposures during firefighting activities can involve a complex mixture of combustion products and decomposition by-products in the form of heated gases, vapors, and particulate matter. The overall characterization of these exposures is difficult due to variability of the composition of the fires (e.g., structural fires contain very different materials than vehicle fires). The composition of the smoke can vary not only due to factors such as the fuel source (e.g., natural and synthetic materials) but also the fire conditions (e.g., oxygen availability, temperature, etc.), resulting in chemical exposures that vary from fire to fire [Kulig, 1991].

Variability in exposures among fires can be great; however, a number of chemicals are commonly found in many fire scenarios. Common combustion products and other job-related exposures encountered by firefighters that may present a cancer hazard include but are not limited to: asbestos, arsenic, benzene, benzo(a)pyrene and other polycyclic hydrocarbons (PAHs), cadmium, chlorophenols, chromium, diesel fumes, carbon monoxide, dioxins, ethylene oxide, formaldehyde, orthotoluide, polychlorinated biphenyls, and vinyl chloride [Schenker,1980; Treitman et al., 1980; Orris et al., 1986; Fitzgerald et al., 1986; Osterloh et al., 1986-1987; Froines et al., 1987; Brandt-Rauf et al., 1988; Bates, 1987]. Also, findings from monitored firefighters during the overhaul phase (fire is extinguished and clean-up begins) of structural fires indicates that short-term exposure limits are exceeded for acrolein, benzene, carbon monoxide, formaldehyde, glutaraldehyde, nitrogen dioxide, and sulfur dioxide (Austin et al., 2001 b,c).

The current knowledge of cancer risk among firefighters is based in large part on the results of thirteen retrospective cohort mortality studies (six United States [U.S.] cohorts and seven international cohorts) and three registry-based cancer incidence studies of firefighters, all published since 1978. The mortality studies were conducted in several U.S. cities including Boston, Buffalo, Philadelphia, Seattle, Portland, Tacoma, and San Francisco, and foreign countries including Canada, Australia, France, New Zealand, Sweden, and Denmark (Table I of the Appendix). The registry-based cancer incidence studies included firefighters employed in the states of Florida and California (Bates et al., 2007; Ma et al., 2006). However, these studies have significant limitations which this research project will address.

- **First,** previous mortality studies of firefighters are small; the average number of firefighters included in the six U.S. cohort studies is 4,202, and only 2,410 for the seven international studies. All thirteen of the previous firefighter mortality study cohorts have fewer than 8,000 firefighters and range in size from 830 in the Paris firefighter study to 7,739 in the study of Philadelphia firefighters. None of the six U.S. studies and only two of the seven international studies collected vital status information past 1989. This has resulted in relatively few person-years at risk (time under observation) available for analysis. The average person-years at risk for the thirteen previous firefighter studies is 67,907, with a range of 8,625 (the study of Danish firefighters) to 204,821 (the study of Philadelphia

firefighters). The average person-years at risk is 111,824 for the six U.S. studies and 31,760 for the seven international studies.

- **Second,** as a consequence of the relatively small cohort size and time under observation the previous firefighter cohort studies have few cancer deaths available for analysis (Golden et al., 1995). Of all the studies, only the Philadelphia study has more than 400 deaths due to all-cancers combined (n=500). Four of the six U.S. studies have fewer than 300 total cancer deaths and the average number of total cancer deaths for the six studies is only 267. All but one of the international studies have fewer than 100 all-cancer deaths combined with an average of 70 (Table I of the Appendix). Only seven of the thirteen mortality studies report prostate cancer mortality (Baris et al., 2001: Demers et al., 1992; Beaumont et al., 1991; Vena and Fiedler et al., 1987; Aronson et al., 1994; Torling et al., 1994; Guidotti, 1993) and only two of the thirteen studies report multiple myeloma, (Baris et al., 2001; Heyer et al., 1990; Aronson et al., 1994) and non-Hodgkin's lymphoma deaths (Baris et al., 2001; Demers et al., 1992). Further, no more than 10 multiple myeloma deaths, 20 non-Hodgkin's lymphoma deaths, and 31 prostate deaths were reported in any of the previous studies.

- **Third,** cancer incidence rather than mortality is a more sensitive outcome measure for cancers with relatively low fatality rates (e.g., testicular, thyroid, bladder, prostate, and Hodgkin's Lymphoma). Three studies examining cancer incidence among firefighters have been conducted in the U.S. and abroad in the past seven years (Bates et al., 2001, Ma et al., 2006; Bates, 2007) and suggest an increased incidence of testicular and thyroid cancers. However, a major limitation of all these studies is that none includes any type of exposure assessment or length of time employed as a firefighter.

- **Fourth,** beginning in the mid-1960s there was a widespread introduction of synthetic building materials, predominantly plastics and organic chemicals, increasing the complexity of firefighter exposures (Lees, 1995). However, previous firefighter studies did not collect vital status information after 1989; therefore it is unlikely that these cohorts have accumulated sufficient person-years to detect cancers with long latency that may have resulted from exposures to these newer building materials.

- **Fifth,** few of the previous studies include exposure surrogate information such as duration of employment, number and type of fires fought, and job duties, making the evaluation of exposure-response relations with all-cause mortality or specific cancer and other disease outcomes less precise. Most previous studies to date have not included exposure metrics that consider factors such as employment duration, number and type of fire, conversion from gas to diesel vehicles, advent of diesel emission controls, and use of protective equipment.

Study Rationale

There are approximately 1.1 million volunteer and career firefighters in the U.S. During firefighting activities, firefighters may be exposed to many combustion products [e.g., polycyclic aromatic

hydrocarbons (PAHs), formaldehyde, benzene, chromium compounds, dioxins, asbestos, particulates, and arsenic]. These exposures have raised concerns of excessive rates of cancer among firefighters. Thirteen retrospective cohort mortality studies (six U.S. cohorts and seven international cohorts) have been published since 1978, and three registry-based cancer incidence studies have been published since 2001. Unfortunately, disease risk estimates are inconsistent, primarily due to small cohort size (all thirteen of the mortality study cohorts have fewer than 8,000 firefighters) and few person-years at risk. None of the thirteen studies collected vital status past 1990, resulting in relatively few cancer deaths available for analysis. Also, few of the cohort studies and none of the incidence studies include exposure surrogate information such as duration of employment, number and type of fires fought, and job duties.

This study will address the limitations of previous studies by 1) increasing the cohort size and follow-up time; 2) will include an evaluation of cancer incidence; 3) provide an improved assessment of firefighter occupational exposures because of utilization of information specific to each department on duration of employment, number of runs, categorization of fires (e.g., structural and vehicular), diesel exhaust controls, and use of protective equipment [e.g., Self Contained Breathing Apparatus (SCBA)]; and 4) establish a valuable cohort that may be used for future studies on the risks of firefighting occupations.

Potential Use of Study Findings

Several practical outcomes will result from the project. The International Agency for Research on Cancer (IARC) has recently classified occupational exposure as a firefighter as "possibly carcinogenic to humans" (Group 2B). IARC assigned this classification because of limited evidence from human studies. The study will provide critical human study information for IARC as they continue to review the carcinogenicity of firefighting. The project results may be used to improve current risk models used by firefighter compensation programs.

Study Objective and Specific Aims

The primary objective of the study is to clarify the relationship between firefighter occupational exposures and cancer. This objective will be achieved by improving upon previous firefighter studies by 1) significantly increasing the study cohort size and person-years at risk and 2) using a more detailed exposure surrogate metric in both the mortality and incidence analyses than are found in previous studies.
The specific aims of the study are as follows:

Specific Aim 1: Assemble a large cohort of firefighters and conduct a retrospective mortality study to determine whether cause-specific mortality patterns among firefighters differ from those of the general U.S. population.

Specific Aim 2: Conduct a study of cancer incidence among the assembled firefighter cohort members to determine whether cause-specific cancer incidence among firefighters differs from that of the general U.S. population.

Specific Aim 3: Determine if a dose-response relation exists between surrogates of exposure [e.g., employment duration, number and type of fire runs, use of personal protective equipment (PPE)] and cause-specific mortality (including cancer) and cancer incidence among the firefighters.

Specific Aim 4: Assess the role of confounders and/or effect modifiers (i.e., fire department location, frequency of fire runs) on any associations observed between occupational exposures and outcomes.

Outcomes of Interest

All fatal events and all incident cancers through 2005 will be examined. Based on a review of existing literature, several site-specific cancers are of *a priori* interest. Cancer sites previously identified by epidemiological studies of firefighters as likely due to occupational exposure such as multiple myeloma, non-Hodgkin's lymphoma, and prostate will be studied. Leukemia, brain, stomach, testicular, and colon cancers, which have been determined to be possibly related to fire exposure, will be examined. Also, all cancers combined, and lung, kidney, and bladder cancers, which have been identified by previous studies as unlikely to be related to firefighting exposures but which are of interest because of plausible relations with common fire exposures, will be re-examined in the analysis due to the increased power of this study.

Feasibility Assessment

A feasibility assessment was conducted to identify United States fire departments with sufficient numbers of career firefighters and the records (personnel, work history, and exposure) necessary to support the study.

The feasibility assessment included the following three steps:

I. Identification of potential fire departments for study inclusion
II. Assessment of records availability
III. Preliminary selection of fire departments.

Identification of potential fire departments for inclusion in the study
Discussions describing the study were held with fourteen U.S. fire departments during 2008. Ten departments representing 21,223 current firefighters indicated a willingness to consider participation in the study. They also agreed to participate in further in-depth discussions with NIOSH personnel to confirm that records necessary for the study are available. The ten departments are as follows:

Department	Number of Current Firefighters
• Los Angeles County, CA.	2,687
• Fairfax County, VA.	1,700
• Washington DC Metro	1,427
• San Francisco, CA	1,800
• Charlotte, NC	1,082
• Chicago, IL	4,881
• Houston, TX	3,877
• Philadelphia, PA	2,475
• Cincinnati, OH	811
• Prince William County, VA	493

A description of each department including, the number of currently employed firefighters, and number of fire runs and service calls is included in Table II of the Appendix (not included in the online version).

Assessment of the availability of records necessary to conduct the study
Conference calls were conducted with each of the nine departments to determine the availability of records necessary to conduct the study. These calls included senior fire department staff in charge of the Operations/Personnel, Medical Clinic, Health and Safety, and Training departments. The conference calls were supplemented by visits to three of the nine departments.

Information was collected confirming the availability of 1) demographic data needed to identify individuals and ascertain vital status and cancer incidence; 2) work history data needed to construct complete and accurate work histories for each firefighter; 3) exposure surrogate information (i.e., employment duration, and the number of calls for service); and 4) other variables that potentially modify exposure including the type of call for service (structural or vehicle fire), diesel emission controls, and use of Personal Protective Equipment (PPE). A summary of the information needed, how it will be used, and its availability is provided in Table III of the Appendix (not included in the online version). The availability of the necessary study information by individual fire department is provided in Table IV of the Appendix (not included in the online version).

Preliminary selection of the departments to include in the study
Careful consideration was given to selecting departments to include in the study. It is of critical importance that the study assembles a cohort of firefighters of sufficient size and person-years at risk to detect rare cancer outcomes. Three departments—San Francisco, Chicago, and, Philadelphia —were selected because they expressed a strong commitment to participate in the project, and have all the necessary records required for the study. It is projected that these three departments will result in a cohort of approximately 36,000 current and retired firefighters employed between 1950 and 2010.

In the event that any of the three primary fire departments are unable to take part in the study, the remaining seven departments (Cincinnati, Houston, Charlotte, Los Angeles County, Fairfax County, Washington DC and Prince William County) are potentially available for substitution. These departments could also be phased into the study at a later date if NIOSH and the U.S. Fire Service want to increase the size of the study cohort in the future.

METHODS

Study Design

Cohort Definition
The study cohort is anticipated to consist of approximately 36,000 current and former career firefighters (full-time uniformed firefighters who have successfully completed firefighter training) employed for at least one day at one of the three fire departments included in the study (San Francisco, Philadelphia, and Chicago) from January 1, 1950, through December 31, 2010. Fire department personnel records will be used to identify the firefighters included in the study. The following dates will be required (and are known to be available) for each worker included in the study: date of birth, hire date, termination date, beginning and end dates for each fire department job, and corresponding fire station assignment. Date of death will also be obtained if a worker is known to be deceased.

Data Collection

NIOSH researchers will visit each participating fire department prior to the beginning of the study to finalize plans to extract and capture the data necessary from department records (known to be available), to identify study cohort members, determine causes of death for known decedents and to estimate occupational exposures. Next, NIOSH staff will visit each participating fire department to collect all necessary records. Due to the sensitivity of the information collected, any electronic data with personal identifiers will be stored on encrypted/password protected laptops and will be transported personally by NIOSH personnel between each site and NIOSH. At NIOSH the information will be coded into work history or exposure assessment database management programs designed to combine the fire departments and cities into one large dataset.

IWSB has decades of experience conducting large multi-site cohort studies and has developed a comprehensive data system to efficiently manage data collected for large studies. The data system for the study will include collected and coded demographic and work history information. The demographic information will include all study participants and information such as the firefighter's name, Social Security number, date of birth, sex, race, date and cause of death (if deceased), vital status, and first and last dates employed. A unique identification code (NIOSH ID) will be assigned for each worker. This unique identification code assigned to each study participant allows for the accurate linkage of demographic and work history information.

The work history file information for each firefighter will include all job titles and specific station assignments held while employed during the study period, with corresponding begin and end dates. This file will also include the annual number and type of fire runs made, dates diesel emission controls were installed, and PPE use for each fire department station. All exposure assessment activities will be done by individuals blinded to each firefighter's disease status.

To ensure the quality and accuracy of the coded information, a quality assurance plan will be established prior to the coding effort. A sample of hard copy records will be randomly selected and compared with the electronic final analytic file developed by NIOSH. The review will be performed by personnel independent to the coding effort.

Vital Status Ascertainment

Follow-up for vital status ascertainment will for each firefighter begin on January 1, 1950, the first date employed at one of the fire departments included in the study, whichever is later, and end on the study end date (the most recent year that NDI cause of death information is available). The primary data sources used to ascertain deaths will be the National Death Index-Plus (NDI-Plus) and the Social Security Administration Death Master File (SSA-DMF). In addition, the SSA's "presumed living" file will be used to confirm that workers not found to be deceased by NDI-Plus are alive as of the end of study date (the most recent year that NDI cause of death information is available).

Underlying and contributing causes of death will be obtained directly from NDI-Plus for workers deceased in 1979 or later. For those who died before 1979, death certificates will be obtained from the states in which death occurred. The state of death will be identified for the majority of deaths before 1979 using the SSA-DMF. Underlying and contributing causes of death prior to 1979 will be coded by certified (contract) nosologists trained by the National Center for Health Statistics (NCHS) in the revision of the International Classification of Diseases (ICD) in effect at the time of death.

NIOSH routinely submits applications to match cohorts with the NCHS's National Death Index (NDI) and Internal Revenue Service (IRS) records. These applications are submitted after the study protocol has been approved by the NIOSH Human Subjects Review Board (HSRB). NIOSH routinely receives updated copies of the SSA's Death Master File (SSA-DMF) and matches cohorts to the in-house copy of this file.

Cancer Incidence

The cancer incidence study will be conducted to more accurately assess the risk of specific cancers of interest with high survival rates (e.g., testicular and prostate). The necessary data on firefighters included in the study will be submitted to the California, Illinois, Pennsylvania, and Florida registries to determine cancer incidence. The dates that laws requiring the reporting of incident cases were enacted in these states are as follows; 1981 for Florida, 1988 for California, and 1985 for both Illinois and Pennsylvania. Additional state cancer registries will be identified by an analysis of the geographic distribution of cohort members and by review of the last known addresses of retirees from IRS records. (NIOSH has unique legislative access to address information from the IRS for the conduct of health studies).

IWSB staff routinely submits applications to cancer registries requesting matching for specific cohorts after the study protocols for those cohorts have been finalized and received HSRB approval. This process will be followed for the firefighter study.

Exposure Assessment

Direct exposure measurement data are not available. Thus, the primary sources of individual firefighter exposure information are the duration of employment in a firehouse and the type and frequency of fire runs that are likely to be experienced by that firehouse. A job exposure matrix (JEM) will be constructed for each fire house that will summarize the main exposure determinants (i.e., employment duration, and fire run characteristics) and modifying factors (i.e., installation of diesel exhaust emission controls, implementation of PPE, and job duties) that are necessary to calculate and assign exposure metrics to individual firefighters for each time period of exposure.

Exposure Determinants:

1. Duration of employment is defined as the time accrued by a study participant in a firehouse as an active firefighter and will be calculated from employment information abstracted from fire department records.

2. It's not possible to determine the exact nature and number of fires worked by each firefighter in the study; rather, this exposure determinant will be estimated from the number of fire runs at each fire station stratified by two fire types, i.e., structural fires and vehicle fires. The exposures in vehicular fires may be both qualitatively and quantitatively different from those in structural fires, due to the use of different materials in constructing cars versus buildings (although there is wide variability in the latter). More importantly, vehicle fires are largely open-space exposures which dissipate fairly rapidly, while structural fires often involved protracted confined-space exposures.

Modifying Factors;

Job duties and certain control measures were known to vary over time and between firehouses. Some of these factors were likely to significantly impact the exposure potential of individual firefighters. Thus, we will collect temporal information on firefighter duties and firehouse control measures in place during the study period. At a minimum, we will record the dates that: 1) controls to reduce exposures to diesel exhaust were installed, 2) the use of self-contained breathing apparatus (SCBA) and other forms of PPE were prescribed, and 3) each job was performed. These data will be used in conjunction with other information to develop modifying factors that account for the temporal variation in exposures.

1. *Installation of Diesel Exhaust Control Systems:* Engineering control improvements included the introduction of diesel exhaust ventilation control in the stations to reduce exposure to diesel particulates generated from running vehicles within the station. The year that diesel exhaust ventilation systems were installed at individual fire stations is available for all the fire departments. The use of gasoline-powered engines versus diesel-powered engines is also known for each department.

2. *Use of Self-Contained Breathing Apparatus:* Fire department records indicate the years that SCBA and other forms of PPE were introduced. Also, the year that four-gas monitoring systems were initiated to determine when SCBA could be safely removed is available for all departments. The four-gas monitors are used to measure primarily carbon monoxide (CO), which is a chemical asphyxiant, and oxygen with regard determining a safe environment to remove SCBA equipment. The requirements for donning and doffing of SCBAs has changed over time due to increased awareness of carcinogens and other potentially hazardous chemicals common to the overhaul phase of fire fighting.

3. *Job Duties:* The work history records available for each firefighter included in the study will allow for the identification and time worked in jobs where firefighters are likely not responding to fires as part of their duties (e.g., administrative), resulting in lower exposures from structural fires and firehouse vehicle emissions.

Final decisions regarding the definition of exposure metrics will be based on an examination of a sample of data collected from the firehouses within each fire department and will precede epidemiologic analysis. The construction of the JEM will provide a more in-depth characterization of exposures than currently identified in the literature.

Statistical Analysis

Standardized Mortality Ratio (SMR) Analysis

The NIOSH Life Table Analysis System (LTAS.NET) will be used to generate expected numbers for all-deaths combined, all-cancer deaths combined, and cause-specific deaths by race and sex, within five-year age and five-year calendar time periods (NIOSH, 2001). Person-years and observed deaths will be accumulated for each of these age and calendar time periods from each firefighter's follow-up begin date through the end of follow-up.

Expected numbers of deaths will be based on U.S. population death rates specific for the race, gender, and 5-year age and calendar time periods. United States expected rates are available beginning in 1940 for most cancers of interest and beginning in 1960 for non-Hodgkin's lymphoma and multiple myeloma. For all outcomes, enumeration of observed deaths and person-years at risk

begin on January 1, 1950, the first date employed at a fire department included in the study, or the date the rate file begins whichever comes last and end at the study end date, date deceased, or date lost to follow-up whichever is earliest. Numbers of deaths observed for each cause will be divided by the expected number of deaths to obtain cause-specific SMRs. The precision of each estimated SMR will be assessed assuming a Poisson distribution, with two-sided 95% confidence intervals.

Standardized Incidence Ratio Analysis

Standardized Incidence Ratios (SIRs), person days at risk, and the expected number of cancer incidence cases will be calculated using the NIOSH Life Table Analysis System (LTAS.NET). The methods for producing these estimates are the same as those used for the mortality analyses. Person-days at risk will accumulate beginning on the date the registry began, the date of first employment, or the date the worker moved to that state, whichever is latest. Each individual contributes person-days until the date of diagnosis of cancer, the date of death from a disease other than cancer, the last date for which registry records are complete, the date he or she moved to another state, or date lost to follow-up whichever is earliest.

Internal Analysis

Because SMRs and SIRs are affected by the age structure of the study population, comparison of SMRs and SIRs for different sub-populations of the cohort can be misleading. Standardized rate ratios (SRRs) allow for comparison within the study populations by weighting observed stratum-specific rates according to a common (internal) standard (Rothman and Greenland, 1998). SRR analyses will be performed for the entire cohort to assess the associations between mortality outcomes and 1) employment duration, 2) total runs, 3) total vehicle runs, and 4) total structural fires runs (Table V of the Appendix, not included in the online version).

For dose-response analysis, a linear trend will be calculated in a person-year weighted regression of directly standardized rates (Rothman and Greenland, 1998). Statistical significance of each trend will be determined using a two-tailed *z*-test with an alpha of 0.05.

Modeling Analysis

Regression analyses will be conducted to further evaluate the relation between occupational exposure and selected outcomes. Risk sets will be defined from the entire cohort of firefighters for each case of interest. Each risk set will include all controls who were under observation and who lived to an age equal to or greater than the age of the case at death. 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 cancer mortality and therefore an important potential confounder of the association of interest in the analyses. All occupational exposures of the controls are truncated at the age attained (minus any lag period) of the case.

Conditional logistic regression analyses will be performed for the entire cohort to assess the associations between mortality outcomes and 1) employment duration, 2) total runs, 3) total vehicle runs, and 4) total structural fire runs. The influence of fire station-specific temporal modifiers will be evaluated in the regression analyses. Statistical and exposure response modeling analyses will be performed using SAS 9.2 (SAS Inc., 1999).

Assessment of potential confounders and effect modifiers

Factors that may confound or modify the association between exposures and outcomes of interest of critical importance are sex, age, calendar year, and smoking status. Regression, SMR, and SRR

analyses will control for age, gender and calendar year. Available fire department records will be examined to determine the availability of smoking information. If adequate smoking information is not available, SMRs for smoking-related illnesses will be investigated to examine the estimated level of tobacco use in the cohort. It is likely that firefighters included in the study have relatively low rates of smoking due to Worker Compensation Presumptive Disability laws covering certain cancers that have been instituted in 24 states and require that firefighters not smoke to qualify for compensation.

Effect modification occurs when the association between the exposure and disease under study varies by levels of a third factor (Hennekens, 1987). It is possible that the exposure and disease relationship in this study may be modified by factors such as type of fire fought (e.g., structure or vehicle), fire department employed, job assignment, and PPE use. Possible effect modification by these factors will be evaluated statistically in the analysis.

Healthy Worker Effect (HWE)

The healthy worker effect, which is less pronounced for cancer mortality has two components, both of potential relevance to studies of firefighters: the healthy worker selection and healthy worker survivor effects. Selection of healthier job applicants into employment through an entry screening test can lead to a downward bias in summary statistics such as the SMR and SIR, which compare a working cohort to the general population. Internal comparisons among firefighters will be utilized in the analysis because that is the most direct way to achieve partial control for the healthy worker selection effect (Checkoway et al., 1989).

The healthy worker survivor effect, which involves retention of healthier workers in the workforce while less healthy workers are eliminated through ongoing workplace screening or illness, remains a problem in internal analyses; the healthy worker survivor effect can cause negative confounding such that long-term workers appear to have lower risk than workers with shorter employment durations. Because recent research indicates that the healthy worker survivor effect can best be mitigated by adjusting for time since termination (Richardson et al., 2004; Steenland et al., 1996), the internal analysis for the study will include an adjustment for this variable.

Power analysis

An artificial cohort of career firefighters was created in order to estimate the power of detecting elevated SMRs for malignant neoplasms of the prostate, other male genital organs, brain and other parts of the nervous system; non-Hodgkin's lymphoma; leukemia; multiple myeloma; and all cancers combined. The cohort definition included all career firefighters in selected fire departments who worked 1 day or more in the period from 1 January 1950 through 31 December 2005. Fire departments were selected from a list of U.S. fire departments with 800 or more career fighter fighters in 2005. Power calculations described here included the fire departments specified in Table VI of the Appendix. For a particular fire department, the artificial cohort was assembled by first including all career firefighters employed in 1950. Firefighters were added to the base cohort as they joined the fire department in subsequent years (1951 – 2005). The cohort definition was modified to include only career firefighters who worked 1 day or more in the period from 1 January 1965 through 31 December 2005 for the Fairfax County Fire and Rescue.

It is estimated that the sample cohort (Table IV of the Appendix, not included in the online version), will result in a cohort of approximately 18,000 current and retired firefighters who meet the stated cohort definition of 1 day or more of work in the period from 1 January 1950 through 31

December 2005 (from 1 January 1965 for Fairfax County). With vital status follow-up through 2005, the expected number of person-years at risk (PYAR) is approximately 470,000. Expected numbers of deaths from malignant neoplasms of the prostate, other male genital organs, brain and other parts of the nervous system; non-Hodgkin's lymphoma; leukemia; multiple myeloma; all cancers combined; and major categories of diseases of the heart and other diseases of the circulatory system are provided in Table VII of the Appendix. These values were used directly to compute power. All calculations assume a 5% type I error rate. The table provides the minimum detectable SMR for a specified power. For example, the minimum detectable SMR for prostate cancer for 80% power is 1.20. It is important to note that the sample size and power calculations are based on mortality.

Study Strengths

The study has several strengths that significantly improve upon completed firefighter studies, enabling a more precise evaluation of the relation between firefighter occupational exposures and cancer.

First, the study will be the largest pooled cohort of firefighters ever assembled for epidemiologic study. The cohort of approximately 36,000 current and former firefighters will be - the largest firefighter cohort ever assembled to date. This cohort of firefighters will provide an unprecedented opportunity to continually update research evaluating the occupational risk associated with firefighting by supporting future mortality, incidence, and nested case control studies.

Second, the study will follow firefighters employed from 1950 through 2010, with an estimated 470,000 person-years at risk. This is more than twice the number of person-years at risk assembled by the largest cohort study to date, significantly increasing the power to detect rare disease outcomes. Further, this will provide sufficient person-years at risk after 1970 to evaluate for the first time the effects of building material changes. It is estimated that approximately 7,103 deaths due to all causes combined (79%) will have occurred after 1970 in this firefighter cohort.

Third, the study will have an estimated total of at least1,920 cancer deaths, which is approximately three times the number of total cancer deaths observed from the largest firefighter cohort study to date. Further, it is projected that there will be more observed deaths from specific cancers of interest: it is projected that this study will have twice the number of multiple myeloma and non-Hodgkin's lymphoma (NHL) deaths, and four times the number of prostate cancer deaths compared to the mortality study of Philadelphia firefighters (the largest study to date of U.S. firefighters). Also, the assembled cohort will support the development and design of future nested case-control studies capable of assessing in greater detail the relation between selected outcomes and occupational exposures.

Fourth, the study will provide a more detailed historical reconstruction of firefighter occupational exposures than most previous studies. The study will examine cancer incidence in addition to mortality. A job exposure matrix that will include over 300,000 fire-related calls for service per year will be constructed and used to qualitatively estimate exposure levels by time, job, number and type of fire run, duration of employment, and use of diesel emission controls and PPE.

Study Limitations

Individuals are required to pass very strenuous physical fitness requirements to become a firefighter and are less likely to engage in unhealthy behaviors such as drug, alcohol, or tobacco use. The result is that the study cohort of firefighters is likely healthier than the general working population, causing healthy worker effect (HWE) bias. The HWE is characterized by lower relative mortality for some disease outcomes in occupational cohorts. However, HWE effects are not as pronounced for cancer mortality outcomes as for some non-cancer outcomes such as cardiovascular disease (CVD) (Checkoway, 1989). Analyses using internal comparisons of firefighters are planned to address this potential bias, but the HWE may still have an impact in this study by lowering mortality risk estimates for some disease outcomes.

Because personal exposure measurements are not available, duration of employment in firefighting jobs will be used as the primary exposure variable for dose response analyses. This is a limitation

because it is not possible to precisely quantify specific chemical exposures or variations in exposures due to factors such as the type of fire and stage of fire. Nonetheless, most previous studies to date have not included exposure metrics that contain factors such as employment duration, number and type of fire, conversion from gas to diesel vehicles, advent of diesel emission controls, and use of protective equipment. Furthermore, the epidemiologic and exposure-related data that are collected, assembled, and examined, will establish a generalizable research platform that promotes future studies on the risks of firefighting occupations.

It is possible that some firefighters may have a second job that is completely unrelated to their firefighting duties. It is possible that while engaged in these jobs, some firefighters are exposed to a variety of chemical compounds linked to specific disease outcomes. While it is beyond the scope of this study to identify outside jobs and quantify resulting potential exposures, it may be possible to conduct such an analysis in future case-control studies.

It is likely that smoking history information for study participants is sparse. Therefore, it is possible that the risk estimates for certain smoking related cancers (which are not the primary cancers of *a priori* interest) may be confounded. If adequate smoking information is not available, SMRs for smoking-related illnesses will be investigated to examine the estimated level of tobacco use in the cohort. Further, it is likely that firefighters included in the study have relatively lower rates of smoking than the U.S. general population due to Worker Compensation Presumptive Disability laws that have been instituted in 24 states.

While this study will include non-white and female workers, it is likely that the study cohort members will be overwhelmingly white and male. Therefore, meaningful analysis of many cancers for females and non-whites may not be possible.

Stakeholder Interest

Numerous stakeholders including members of congress, several large metropolitan fire departments, IARC, the IAFF, IAFC, the National League of Cities, and the Firefighter Cancer Support Network have expressed an interest in a multisite study of cancer among U.S. firefighters.

This study will advance the following goals: the NORA Services and Public Safety Sector Council research goal to develop a peer-reviewed protocol to conduct epidemiologic studies of chronic disease among fire service personnel, including retirees, and to complete epidemiologic analyses of chronic disease and evaluate relations between disease risks and occupational exposures among firefighters by 2013; and the NORA Cancer, Reproductive Health, and CVD cross-sector goals of conducting research to reduce work-related cancer by identifying associations between cancers and workplace exposures. The recommended actions for worker protection resulting from this research will be communicated to scientists, regulatory agencies, other stakeholders, and the public via scientific journal articles, public meetings, and presentations.

Finally there will be two practical outcomes important to stakeholders resulting from completion of the study. First, IARC has recently classified occupational exposure as a firefighter as “possibly carcinogenic to humans” (Group 2B). IARC assigned this classification because of limited evidence from human studies. The study will provide critical human study information for IARC as they continue to review the carcinogenicity of firefighting. Second, the study results may be used to improve current risk models used by firefighter compensation programs.

In collaboration with the IAFF, the IAFC, and the Firefighter Cancer Support Network, the findings and recommendations of this study will be communicated to other firefighter organizations (United States Fire Administration, National Volunteer Fire Council, and National Fire Protection Association). In addition, risk communication and health communication techniques will be applied to communicate the findings to front-line firefighting personnel. Based on study results, the communication plan may be further expanded to include a social marketing campaign; this campaign would be treated as a study in itself and would require additional NORA funding to be completed.

The recommended actions for worker protection resulting from this research will be communicated to scientists, regulatory agencies, other stakeholders, and the public via scientific journal articles, public meetings, and presentations.

Study timeline

FY 2010 Goals: Complete tripartite review & Human Subjects Review Board approval of study protocol. Finalize worker rosters at selected fire departments.

FY 2011 Goals: Initiate collection and coding of demographic and work history information. Initiate vital status and cancer incidence determination for the cohort. Initiate exposure assessment work.

FY 2012 Goals: Complete data collection, exposure assessment work, vital status and cancer incidence determination. Initiate mortality and cancer incidence analyses.

FY 2013 Goals: Complete the mortality and cancer incidence analyses. Complete draft manuscripts of both mortality and cancer incidence analyses. Communicate the epidemiologic results to stakeholders, the public and workers.

Human Subjects Involvement and Characteristics

Protection of Human Subjects

Work history, demographic, and medical history information will be collected for firefighters included in the study. The records collected will contain social security numbers (SSNs) which will be protected and used only for matching with other record systems, such as the NDI.

Gender and Minority Inclusion

This is a records based study. No children will be included in this research. The proportion of women and minorities in the study, for each department, is not precisely known prior to data collection, but all available female and non-white firefighters will be included in the study. The U.S. Fire Service estimates that currently 2% of U.S. firefighters are women and 4% are non-white. For the study it is estimated that there will be 720 female firefighters and 1,440 non-white firefighters included in the cohort. Due to the projected limited number of women and non-white firefighters, separate analyses for these groups are likely not feasible, but they will be included in the full-cohort analyses. No study subjects will be contacted during the course of the study. A limited number of current firefighters may be contacted to only provide general information about work practices.

Confidentiality, Retention, and Disposition of Records

Privacy Act

All information obtained for this study will become part of the CDC Privacy Act System (09-20-0147, "Occupational Health Epidemiologic Studies"). Personal identifiable information will be protected at NIOSH per requirements of the Privacy Act. The data will be held at the NIOSH facility, with access monitored and restricted to the research team.

Summary of 308 (d) Assurance of Confidentiality

NIOSH has received authorization under Section 308(d) of the Public Health Service Act (42 U.S.C. 242 m (d)) to give assurance of confidentiality for death certificates and the information thereon and cancer registry records. NIOSH will not release 308 (d)-protected information to anyone without the written consent of the states or agencies which provide this information. No one except NIOSH employees and their contractors will be allowed to see or have access to the information. These individuals will be required to handle the information in accordance with procedures outlined in the CDC Staff Manual on Confidentiality and to follow the specific procedures documented in the Confidentiality Security Statements.

When not in use by authorized project staff, all hard copy material and physical media containing confidential data will be stored in locked containers, file cabinets, or rooms. Access to locked storage areas will be limited to authorized project staff. This procedure will apply to all physical media containing confidential data, including data collection forms, and printouts. Staff working with confidential materials during forms processing and data handling will have access only to the materials that they are currently processing.

Electronic files containing programs, documents, or sensitive data will be stored on computer systems that are protected from accidental alteration and unauthorized access. Electronic files, whether they are stored on the CDC network, the CDC mainframe computer, or the contractor's network will be protected by user identification and authentication. Access to study files will be limited to those with a need to access the data. Routine daily backup procedures are in place. Backup files will be stored in secure on-site and off site facilities.

The CDC/Atlanta Data Center and the NIOSH LAN comply with several Federal policies, statutes, regulations, and other directives for the collection, maintenance, use, and dissemination of data, including the Department of Health and Human Services (HHS) Automated Information Systems Security Program and the Computer Security Act of 1987 (Public Law 100-235). Additionally, both centers are in compliance with The CDC network and CDC staff operate in compliance with Federal policies, statutes, regulations and other directives for the collection, maintenance, use, and dissemination of data, including Federal Information Security Management Act of 2002, Secure One HHS Standards and Guidance, and the CDC Office of the Chief Information Security Officer Policies, Procedures and Guidelines. Everyone with access to CDC network systems takes annual security and awareness training. User authentication is administered with strong password policies and variance detection. CDC maintains a secure network with appropriate controls, such as firewalls, virus detection, and intrusion detection.

Disposition of Records at Completion of Study

Upon completion of this study, data will be archived according to National Archives and Records Administration recommendations.

Risks to Subjects

1. Sources of Materials
This is study is restricted to use of existing data and records on subjects.
Potential Risks:
The sole risks to participants are related to privacy of personally identified data.

2. Adequacy of protection against risks
Recruitment and informed consent:

The justifications for a waiver of consent for this study are as follows:

1) Minimal risk --this study is of minimal risk to the study subjects because it is a records based study with no contact with any of the study subjects. Because some personal confidential information will be collected there is the possibility of a breach in access to confidential information; however the risk of this is minimal.

2) No adverse affects --the waiver requested will not adversely affect the rights or welfare of the study participants.

3) Research not practicable otherwise--this research can not be practicably carried out with out the waiver because many of the study participants are deceased.

4) Follow-up information available--the study results will be communicated with living study participants by published journal articles and public meetings.

Protection against risk:
Risks to subjects are restricted to privacy of personally-identified data. Therefore, risk protection measures are focused on ensuring the protection of these data. Please see description above of 308d and the Privacy Act.

3. Potential benefits of the proposed research to the subjects and others
This proposed research will identify and evaluate occupational risks that may increase cancer incidence and mortality among career firefighters in the U.S. The proposed research will by clarifying the relationship between firefighter occupational exposures and cancer lead to interventions with the potential to reduce morbidity and mortality.

4. Importance of the knowledge to be gained
The risks to the subjects are limited to data privacy issues. With adequate data protection measures in place, these risks should be minimal. This research has the potential to influence regulatory bodies (e.g., state worker compensation programs) and international research organizations such as IARC.

Ethics Verification

All NIOSH researchers possess current CDC ATSDR scientific ethics verification.

Notification of Group Results

Study results are disseminated to workers or their representatives in accordance with stated NIOSH Notification Guidelines (National Institute for Occupational Safety and Health 1995) and the protocol HSRB 90-DSHEFS-09 "General Plan for Notification of Subjects of NIOSH Epidemiologic Studies Conducted After July 1, 1988 and Industrial Hygiene Studies Conducted After October 1, 1989." Notification is led by a Notification Officer who in consultation with the Project Officer determines the level of notification (workplace posters, study results to industry and union representatives, and/or individual letters to surviving members of the cohort). After the Notification Officer, in consultation with the Project Officer, develops the notification message, that message is cleared by the division director (of the division leading the project) under notification protocol procedures.

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APPENDIX

Table I: Firefighter Mortality Studies—United States and International Conducted Since 1978

United States Firefighter Mortality Studies

Author	Fire Department Location	Study Population	Study Dates	All Cause Deaths	All Cancer Deaths	Vital Status FU
Baris et al., 2001	Philadelphia	7,789 white males	1925 - 1986	2,220	500	1986
Demers et al., 1992	Seattle, Tacoma & Portland	4,546 white males	1944 - 1989	1,169	291	1989
Beaumont et al., 1991	San Francisco	3,066 white males	1940 - 1970	1,186	236	1982
Heyer et al., 1990	Seattle	2,289 white males	1945 - 1980	383	92	1983
Vena et al., 1987	Buffalo	1,867 white males	1950 - 1979	470	102	1979
Musk et al., 1978	Boston	5,655 white males	1915 - 1975	2470	367	7/75

International Firefighter Mortality Studies

Author	Fire Department Location	Study Population	Study Dates	All Cause Deaths	All Cancer Deaths	Vital Status FU
Bates et al. 2001	New Zealand	4,305 (4,221 males, 84 females) All White	1977 - 1995	117	42	1996
Deschamps et al. 1995	Paris, France	830 white males	1977 - 1990	32	18	1990
Aronson et al. 1994	Toronto, Canada	5,414 white males	1950 – 1989	777	199	1989
Tornling et al. 1994	Stockholm	1,116 white males	1951 - 1986	316	93	1986
Guidotti, 1993	Alberta Canada (Edmonton or Calgary)	3,328 white male firefighters	1927 - 1987	370	92	1987
Hansen, 1990	Denmark	886 white males	1970 - 1980	57	21	11/1980
Eliopulos et al. 1984	Western Australia	990 white males	1939 - 1978	116	30	1978

Table VI: Fire departments included in the artificial cohort

Fire department	Size in 2007	Cohort begin year	Size in begin year [a]	Total size [a]	Person-years at risk [a]
Chicago Fire Department	4881	1950	3919	8400	220,000
Fairfax County Fire and Rescue, Fairfax, VA	1700	1965	1449	2500	63,000
District of Columbia Fire Department, Washington D.C.	1427	1950	1216	2500	64,000
Los Angeles County Fire Department, Los Angeles, CA	2687	1950	2157	4600	120,000
All fire departments combined	10,695	---	8,741	17,627	455,000

[a] Estimated size in begin year assumes 1.0% loss and 1.4% gain each year; total size includes all firefighters employed in cohort begin year plus all firefighters hired through 2005; PYAR includes time at risk from the risk begin date through the assigned date last observed.

Table VII: Estimated power for the artificial cohort assembled from the fire departments in Table VI

Underlying cause of death	Expected number of deaths	SMR detectable with specified power[b] 80%	SMR detectable with specified power[b] 90%	Range of Elevated Risk Estimates among Firefighters Reported in Meta-Analyses [c]
All cancers	1,920	1.06	1.07	5% -9%
Cancer of prostate	190	1.20	1.23	27% - 28%
Cancer of the brain and other parts of the nervous system	44	1.42	1.50	20% - 43%
Non-Hodgkin's lymphoma	65	1.35	1.41	36% - 51%
Leukemia	71	1.33	1.39	12% - 30%
Multiple myeloma	31	1.52	1.62	50% - 51%

[a] Assuming a 5% type I error rate

[b] Table entry is the minimum detectable SMR assuming a 5% type I error rate and the specified power

[c] Reported in meta analyses conducted by Lemasters et al., 2006; Howe and Burch 1990; Samet et al., 2005 and by IARC, 2007