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An Occupational Health Investigation of Cancer Among Fire Fighters in Anne Arundel County, Maryland

Submitted by:

Jonathan M. Samet, M.D., M.S.
Professor and Chair
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe St., Suite W6041
Baltimore, MD 21205

and

Nrupen Bhavsar, M.P.H.
Senior Research Assistant
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe St., Suite W6033
Baltimore, MD 21205

INTRODUCTION

This report provides the findings of a ten-month study of a possible cancer cluster among fire fighters in Anne Arundel County, Maryland. Fire fighters are exposed to smoke generated by the combustion of diverse materials, and the smoke is known to contain carcinogens. Consequently, several decades of research have been directed at risk for cancer among fire fighters, as well as for other chronic diseases, particularly non-malignant respiratory diseases. This report originated with a specific request from the Maryland Department of Health and Mental Hygiene (DHMH) concerning a possible cancer cluster among fire fighters in Anne Arundel County. The exposure of specific concern was to smoke generated by training fires at the Anne Arundel County Training Facility. For a period of 9 years, reportedly from 1971-1979, the training fires used waste oils provided by BGE that were contaminated with polychlorinated biphenyls (PCBs). Consequently, a substantial number of fire fighters and instructors were exposed to PCBs and compounds generated by their combustion.

This report covers a range of topics and activities relevant to interpreting the possible cancer cluster. These activities included characterizing the cluster and evaluating potential exposures to PCBs and their combustion by-products of fire fighters who participated in training fires at the Academy, assessment of applicable scientific literature, and consideration of research that might provide greater insight into the risks sustained by fire fighters. Preliminary recommendations are also offered with regard to medical monitoring.

THE JOHNS HOPKINS INVESTIGATION

History of inquiry

In June, 2004, the Maryland DHMH asked the Johns Hopkins Bloomberg School of Public Health to investigate a possible cancer cluster among fire fighters in Anne Arundel County, Maryland. The request was directed to Jonathan Samet, M.D., M.S., Professor and Chair of the Department of Epidemiology and a pulmonary physician and epidemiologist who has addressed occupational and environmental causes of cancer. The Bloomberg School of Public Health contracted with the DHMH to 1) generally investigate the cancer cluster, and 2) specifically to carry out a series of activities related to the cluster in a nine-month study (July 1, 2004-March 31, 2005) that was subsequently extended to 10 months. The specific charge to Johns Hopkins was broad:

> "The Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology (JHU), shall conduct an occupational health investigation to analyze cancers among fire fighters in Anne Arundel County, Maryland. This investigation will be led by Dr. Jon Samet on behalf of the Maryland Department of Health and Mental Hygiene (Department)."

This scope of work was defined with the development of a project work plan that guided project activities (Appendix A). In the work plan, two major goals were established. The first was to assess the feasibility of a formal epidemiologic study of the risk for cancer incidence and mortality among Anne Arundel County fire fighters. The second goal was to prepare a final report that discusses available information about cancer risks in fire fighters. The elements of the work plan included a methodology for the proposed literature review of: 1) cancer in fire fighters; 2) cancer risk associated with exposure to PCBs; 3) brain cancer among fire fighters; and 4) biomarkers of exposure or outcome. The work plan went on to

describe the steps to be taken to characterize the cancer cluster and how the feasibility of further research would be addressed.

Chronology of Study Activities

Initially, background information was gathered from the Anne Arundel County Fire Department and from the fire fighters and their representatives. To gain an understanding of the concerns of fire fighters, their families, and other stakeholders, a meeting was held at the Anne Arundel County Firehouse on August 4, 2004. Representatives from the fire fighter union groups (Anne Arundel County Professional Fire Fighters Local 1563, Anne Arundel County Retired Fire Fighters Association, Anne Arundel Volunteer Fire Fighters Association, and Professional Fire Fighters of Maryland), current deputy chiefs from the Anne Arundel County Fire Department, and the Johns Hopkins team attended the meeting. Union representatives explained the history of the Anne Arundel Training Academy, including the training exercises and training fires carried out at the facility. Of concern to the union representatives was the occurrence of cancers in fire fighters who completed their training at the Academy, in particular an apparent cluster of brain cancer. The groups were also concerned about exposure to smoke from combustion of oil contaminated with PCBs; the oil had been donated by BGE to the Academy for use in training fires (see Appendix B for description of the training fires).

A second meeting in the form of an open forum was held on October 18, 2004, at Old Mill High School in Anne Arundel County. Various union representatives, current and former fire fighters, families of deceased fire fighters, representatives from the DHMH, lawyers, reporters, and the Johns Hopkins team attended the meeting. Dr. Samet presented, through PowerPoint slides (Appendix C), the background of the investigation into the possible cancer

cluster in Anne Arundel County fire fighters and the current status of the project. The contents of the slides included a description of a cancer cluster, how researchers investigate clusters, and why they occur. Furthermore, the scope of the planned investigation was discussed, including examples of an evidence table and forest plots from the literature review then in progress. Following the presentation, Dr. Samet addressed questions posed by the audience, which centered on the following topics:

1. Why is the investigation limited to fire fighters from Anne Arundel County?
2. Does Johns Hopkins have enough resources for the study (people, money, time)?
3. What is the current status of the investigation and what are the next steps?
4. How can the various stakeholders assist in the investigation?
5. How will the state use the initial report and what is the timetable for action?

EXPOSURES OF FIRE FIGHTERS

Overview

On a regular basis, fire fighters encounter physical, chemical, and psychological exposures associated with increased risk for disease and death. A primary concern is inhalation of toxic and asphyxiant materials in smoke along with risk for smoke-induced damage to the upper and lower respiratory tracts. Physical exposures include heat, excessive exertion and strain from carrying objects or people, as well as impact and other environmental stressors including noise. There is potential for emotional stress from responding to emergencies, being placed repetitively at risk for injury and death, witnessing fire victims, and being responsible for someone else's life [1]. Chemical exposures are unavoidable, stemming from inhalation of smoke generated by the combustion of diverse materials and also

from releases of materials within burning structures or from accidents. Chemical exposures may increase risk for cancer and for other diseases, including acute and chronic lung disease.

General Inhalation Exposures

Combustion can lead to smoke formation, and inhalation of smoke may be associated with diverse risks to health. Compounds identified in the particulate (solid) phase of smoke include carbon particles, silica, fluoride, aluminum, lead, acids, bases, and phenols [2]. In a study by the National Institute for Occupational Safety and Health (NIOSH) of 22 fires -- mostly residential -- , total particulate concentrations were reported to range from not detectable to 560,000 $\mu g/m^3$ during the knockdown phase and from not detectable to 45,000 $\mu g/m^3$ during overhaul [3]. Such high concentrations, however, could not be tolerated without protection or only fleetingly. By comparison, the 24-hour average PM_{10} (particulate matter less than 10 μ in aerodynamic diameter) in Anne Arundel County on March 28, 2005 was 21 $\mu g/m^3$ (http://www.epa.gov/air/data/geosel.html), equivalent roughly to a total particulate level of 42 $\mu g/m^3$, considering particles of all sizes. Another potential source of exposure to particles is exhaust emission from diesel engines in fire fighting vehicles. In a study of airborne particle levels in firehouses, average concentrations were predicted to be 300 $\mu g/m^3$, of which 225 $\mu g/m^3$ were estimated to be from diesel exhaust, while the rest could be attributed to background and cigarette smoke [4].

Inhalation exposures of fire fighters have changed considerably in recent decades due to the proliferation of plastic-containing materials. It has been estimated that in the United States alone, 30 billion pounds of plastics are produced annually [5]. Combustion and degradation from heat can cause plastics to release toxic fumes and gases. These fumes are often invisible or produce a thin fog-like haze, and appear innocuous. However, these fumes can be extremely toxic and carcinogenic [5].

Hydrogen chloride, as either an aerosol or a gas, is another by-product of the decomposition of chlorine-containing compounds (plastics and some flame-retardant chemicals). Even as use of plastics increases, hydrogen chloride detection is relatively infrequent in studies of fire fighter exposure [6]. In the NIOSH study, hydrogen chloride was detected in two samples from 22 fires [3].

Hydrogen cyanide is a toxic gas produced from the combustion of nitrogen-containing polymers and from the combustion of paper, silk, and wool. In the NIOSH study of 22 fires, hydrogen cyanide was detected during the knockdown phase (phase when the main body of fire in brought under control) in 12 fires and during the overhaul phase (search for and extinguish hidden fires) in three fires [3]. Concentrations in these two phases ranged from non-detectable to 23 ppm and non-detectable to 0.4 ppm, respectively. Three samples collected exceeded the 10 ppm short-term exposure limit (STEL) in the knockdown phase [6].

Carbon dioxide can act as an asphyxiant at sufficiently high concentrations. It is present in fire environments in concentrations from normal background levels (350-400 ppm) to elevated levels of 100,000 ppm in test fires. Measured in a relatively small number of studies, carbon dioxide concentrations have been found to be high in self-contained breathing apparatus (SCBA) masks, suggestive of increased metabolic activity from strenuous activity and not environmental factors [6].

Carbon monoxide, a fairly common and acutely toxic contaminant, is a product of incomplete combustion that is prevalent during the earlier phases of combustion and during fire suppressions when temperatures are generally lower [6]. Exposure to carbon monoxide, even at low concentrations, can lead to poor judgment, decrease in visual acuity, and poor decision-making. Multiple studies have reported carbon monoxide concentrations in excess of 500 ppm [7 8]

and some have reported concentrations approaching the short-term lethal concentration of 5000 ppm [9].

Sulfur dioxide can form from the combustion of sulfur-containing substances. Water used in fire suppression can react with sulfur dioxide to form sulfuric acid. Studies have measured sulfur dioxide concentrations ranging from not detectable to 41.7 ppm [6]. Acute exposure to concentrations of 100 ppm is considered life-threatening [10].

Acrolein, an irritant, can be produced from the combustion of wood, cotton, paper, and plastics containing styrene and polyolefins. Measurements of acrolein concentrations range from not detectable to 3.2 ppm in the NIOSH study, with levels of 5 ppm immediately dangerous to life or health. In gaseous form, it can cause death in a relatively short period of time to unprotected individuals [6].

Benzene is detected in almost all fires because of its presence in everyday household products and because it is produced from the combustion of wood and plastic [6]. Measured concentrations in the NIOSH study range from not detectable to 22 ppm during the knockdown phase and not detectable to 0.3 ppm during overhaul.

Of course, combustion may generate myriad other compounds, depending on the materials burning and the conditions.

Polychlorinated Biphenyls

Of particular concern in this investigation are PCBs, heavy, oily liquids with chemical properties (high boiling point, chemical stability, low flammability, and heat resistance) that have made them useful in certain industries. There are multiple PCB compounds, theoretically up to 209, based on the chlorinated positions of the rings (Figure 1); only 60 to

90 have been in the mixtures used in actual chemical applications. Toxicity may depend on the physical conformation of the particular congener.

When Congress banned the production of PCBs in 1977, millions of pounds of PCBs were still in active use due to their ubiquitous presence in buildings, television sets, transformers, fluorescent lights, home air conditioners, hydraulic fluids, paints, sealants, and in the production of plastics [5]. Nearly 30 years later, these compounds are found far less frequently. Unfortunately, the chemical properties that make them useful in these applications also make them resistant to chemical and biological degradation. Destruction of PCBs can be achieved through high temperature incineration, but known byproducts of PCB incineration (polychlorinated dibenzodioxins and polychlorinated dibenzofurans) have been classified as carcinogenic [5].

Because of their dielectric properties, PCBs were widely used in transformers and capacitors, until phased out in the late 1970s. Combustion by-products of PCBs became a concern because of several transformer fires that led to contamination of buildings by both PCBs and compounds generated by the fires [11-16]. Because of these fires and other concerns about combustion of PCBs, there is substantial literature on the compounds generated by combustion of PCBs. From both laboratory experiments and follow-up studies at fire-contaminated sites, formation of polychlorinated dibenzo-*p*-dioxins has been well-documented [17-20]. These compounds have both toxic and carcinogenic activity [21-27].

Fire fighters may be exposed to PCBs directly in one of three ways: inhalation of air vapors, mists, or particles containing PCBs; absorption through skin and eyes; or ingestion of contaminated material. Each of these pathways has been demonstrated to be an effective route for PCBs to enter the body and each is relevant to the training fires. Inside the body, PCBs circulate through the blood and are stored in adipose tissue. Distribution, metabolism, and

half-life vary across the various congeners, depending on their properties. Half-lives of various congeners have been measured in several populations (Table 1) [28-30]. They are as brief as six months and as long as 5-6 years.

Evidence on the carcinogenicity of PCBs comes from three lines of research: animal bioassays, studies of workers, and studies in the general population. Animal models have shown evidence of carcinogenicity, but their findings are of uncertain relevance to human exposures. Human evidence of carcinogenicity is limited, but associations between exposure and cancer have been found in occupational studies of cancer mortality in workers exposed to PCBs. They have been associated with risk for a number of cancers in epidemiological studies [5]. Published studies of occupational exposure to PCBs have focused on capacitor and transformer workers with high exposures. These studies have reported elevated rates of brain [31], gastrointestinal tract [32], biliary tract, liver and gallbladder [32;33; 34], malignant melanoma [31], and hematologic neoplasms [32]. The study populations are generally small and consequently a number of the reported associations are not statistically significant and the evidence is not consistent across the studies. Table 2 lists studies of workers reporting on the association of occupational PCB exposure with cancer risk [31-38;38] . Case-control studies have been conducted in the general population to examine associations between cancer and past exposure [27].

The International Agency for Research on Cancer (IARC) of the World Health Organization last reviewed the carcinogenicity of PCBs in 1978, determining that the evidence for carcinogenicity to humans was *limited*, and to animals as *sufficient*. Consequently, PCBs were placed into Group 2A, as probably carcinogenic to humans [21]. This classification has not been updated subsequently. The National Toxicology Program of the U.S Department of Health and Human Services found that several mixtures of PCBs are

"reasonably anticipated to be a human carcinogen" based on evidence from animal models [39] , although evidence for carcinogenicity of PCBs in humans is inadequate [39].

SYSTEMATIC REVIEW OF STUDIES OF CANCER IN FIRE FIGHTERS

Methods

A systematic review involves the identification and evaluation of the full body of literature relevant to a particular topic. The methodology includes the identification of all publications through an organized search strategy and the capture of all relevant findings in a data base [40].

To establish a foundation of evidence for interpreting findings among the Anne Arundel County fire fighters, a comprehensive literature search was conducted of English-language journals with the MEDLINE database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed , January 1966- September 2004) for two sets of articles pertinent to this investigation: 1) cancer mortality in fire fighters; and 2) the association between work in various occupations, including being a fire fighter, and risk for brain cancer. Reference lists from articles found in the search were also reviewed to obtain any additional citations.

The literature searches were carried out in a stepwise manner with steps following a common study selection format. The first iteration involved reviewing studies of cancer mortality in fire fighters. A list of search terms was created to aid in the review process. These terms and the number of titles returned are listed below:

Cancer	N=1,615,360
Fire fighters	N=413
Fire fighter	N=91
Cancer + fire fighters	N=35
Mortality + fire fighters	N=8

A total of 547 abstracts (413+91+35+8) were reviewed for relevance to the subject matter. Articles were included in the review summary if they reported cancer risk estimates for urban fire fighters, but not for wild land fire fighters, and if the report addressed risks of harmful exposures encountered while performing firefighting duties (i.e., not studies on genetics). Articles were excluded if they did not meet these criteria, were not written in English, or were duplicate reports on the same study group. After these exclusions and further evaluation, a total of 26 articles were included in the review summary.

The same approach was used for the search on occupation and brain cancer. For this search, the terms and the numbers of titles returned were:

Cancer	N= 1,614,196
Brain	N= 883,889
Case-control	N= 121,534
Brain cancer	N= 74,971
Gliomas	N= 35,206
Occupation	N= 27,773
Cancer and occupation	N= 2,652
Employment and brain cancer	N= 121
Brain cancer and occupation	N= 111
Jobs and brain cancer	N= 84
Fire fighters and brain cancer	N= 2

We reviewed 318 abstracts (121+111+84+2) for relevance to the topic. Inclusion criteria for this iteration of the search consisted of reporting risk estimates for the association between brain cancer and occupation. Articles were excluded from review if they did not meet the search criteria, were not written in English, or were duplicates. After these exclusions and further review, findings of 17 articles were included in the summary for occupation and brain cancer. In both iterations of the search, references from full text articles read were reviewed for additional citations.

One reviewer (NB) assessed 865 titles and abstracts for relevance to the topic at hand. Information from 43 articles (26 in the first iteration and 17 in the second iteration) was extracted; variables extracted from relevant articles include authors' names, year of publication, population studied, study design, risk estimate, confidence interval or p-value, cancer site, exposure, and occupation.

Researchers often use the standardized mortality ratio (SMR) to describe the level of risk in occupational studies. An SMR is the ratio of the number of observed deaths in a study group (e.g. fire fighters) or population to the number of expected deaths if the study group had the same mortality rates as a standard population, often selected to be the general population in the location(s) where the study was carried out [41]. Values above 100 indicate greater risk and below 100 lesser risk.

Variation in SMRs can result from chance alone, and results of small studies are particularly variable. The width of the confidence interval around the estimate in a study, which captures this variation, is informative as to the amount of information provided by a study. A study with a larger confidence interval has a smaller weight than a study with a smaller confidence interval.

One approach to account for chance variation is to pool data from individual studies into an aggregate estimate [42], using an approach generally referred to as "meta-analysis." Using this approach, studies contribute proportionately more to a pooled estimate based on the amount of information in the study. Studies with larger numbers of participants and outcome events (e.g., deaths from brain cancer) contribute more to the pooled estimate than studies with smaller numbers of participants and outcome events. In this review, we utilized an inverse-variance weighted average computed in STATA using the "meta" command [43]; that is, each study contributed to the overall summary based on its information content.

Findings of Studies of fire fighters

Studies reporting cancer mortality rates in fire fighters and previous exposure to PCBs can be placed into two general categories, retrospective cohort studies and occupational case-control studies (Appendix D). Retrospective cohort studies use historical data to track disease rates among fire fighters in the past; case-control studies involve comparison of exposures (e.g., fire fighting) in people with a particular disease (e.g. brain cancer) and controls, similar to the cases, but without the disease.

Retrospective cohort studies of fire fighters have been conducted in various locations including Toronto [1], Boston [44], Philadelphia [45], Seattle and Portland [46], Paris [47], Australia [48;49], New Zealand [50], Buffalo [51], Canada [52], and San Francisco [53]. Population samples in these studies range from as small as 973 fire fighters in one of the Australian studies [48] to as large 7,789 fire fighters in the study by Baris et al. study of fire fighters from Philadelphia [45].

Occupational case-control studies have been smaller in size, ranging from 315 [54] to 1,883 [55], but the case-control design is statistically efficient and particularly informative at these sizes . Most have reported cancer risks for PCB-exposed individuals employed in a broad array of occupations, with fire fighters being a subset of those occupations. The subsequent material reviews the findings for different causes of death, including specific cancer sites. The pooled estimates and confidence intervals are given in Table 3.

***All-Cause Mortality*:** Studies in this review reported lower risk for dying from all-causes together in fire fighters when compared to other male populations, with standardized mortality ratios (SMRs) ranging from 52 in Parisian fire fighters [47] to 99 in Danish fire fighters [56]. Fire

fighters in the United States had SMRs ranging from 76 in fire fighters from Seattle [57] to 96 in fire fighters from Philadelphia [45]. The finding of an SMR below 100, i.e., a better survival than expected, is generally attributed in worker populations to a phenomenon referred to as the "healthy worker effect" [5]. This form of bias occurs because people who are employed are less likely to have diseases than those who are not employed. The healthy worker effect would be expected for fire fighters who are required to pass strict physical tests and participate in annual physicals. A pooled estimate of 90 was obtained by combining the risk estimates from the studies in the review (Table 3). This figure supports the proposition that fire fighters are healthier than the general population.

***All Cancer Mortality*:** Risk for cancer due to all causes was significantly higher in fire fighters than the comparison populations. Guidotti et al. reported a significantly elevated SMR of 127 in fire fighters in two cohorts from the cities of Edmonton and Calgary in Alberta, Canada [52]. In a study of 205 male fire fighters with at least one year of service in the City of Honolulu Fire Department, Grimes et al. reported an SMR of 119 (not significantly increased) [58]. A significantly elevated SMR of 109 (95% CI: 106-111) was obtained when all of the studies were pooled for this systematic review. Studies have also reported cancer by specific sites and the findings are reviewed below.

Brain cancer: Epidemiological studies of brain cancer have shown risks to be elevated in fire fighters (Figure 2). Guidotti et al. reported three cases of brain cancer among 3,328 fire fighters from Edmonton and Calgary, in Alberta, Canada, [52], about 50% greater than expected. The SMR for fire fighters from these two cities was 147 (95% CI: 30-429) compared to the general male population from the province of Alberta. Similarly, elevated but non-significant SMRs have been reported for fire fighters from Seattle and Tacoma [46], and Stockholm [59]. Significantly elevated SMRs of brain cancer in studies of fire fighters range

from 201 (95% CI:110-337) in 5,995 fire fighters from Toronto [1] to 378 (95% CI: 122-1171) in 205 fire fighters from Honolulu, Hawaii [58]. When mortality studies for brain cancer were pooled, a significantly elevated SMR of 130 (95% CI: 110-151) was found.

***Bladder Cancer*:** Significantly elevated SMRs of mortality were reported for bladder cancer. Among 315 male fire fighters, Sama et al. reported an SMR of 159 (95% CI: 102-250) compared to males from the general statewide population [54]. In a study of 1,867 male fire fighters from Buffalo, Vena et al. reported an SMR of 286 (95% CI: 130-540) compared to the general population [51]. Vena et al. further reported that fire fighters with greater than 40 years latency (i.e., years passed since first employed) between exposure and disease had significantly higher ($p< 0.01$) SMRs (SMR= 453 in fire fighters with 40-49 years latency and SMR= 638 in fire fighters with 50+ years latency) [51]. The findings from Guidotti et al. support these results [52]. Among 3,328 fire fighters from Canada, those with 40-49 years of latency had a significantly ($p<0 .01$) elevated SMR of 1,390. The SMR climbed to 1,700 ($p<0 .01$) in individuals with an exposure index ≥10. The exposure index accounted for some members of a fire squad having greater exposure than others. With the index (exposure weight x years served), a lieutenant or captain had the greatest exposure weight (weight = 1.0), while a district chief had the lowest exposure weight (weight=0). A significantly elevated SMR of 123 (95% CI: 105-144) was calculated when estimates from studies reporting bladder cancer rates were pooled.

***Colon*:** In the reviewed studies, colon cancer rates were significantly elevated among fire fighters. The highest overall colon cancer risk estimates were reported by Ma et al. for African-American fire fighters (mortality odds ratio= 210, 95% CI: 110-400) [55]. Vena et al. reported that fire fighters had an SMR over 80% higher for colon cancer (SMR=183), in comparison with males in the general population [51]. This SMR increased to 265 ($p< 0.01$) for fire fighters with 40-49 years of latency. The SMR increased to 471 ($p<0.05$) for fire fighters

with more than 40 years of experience. The results from Baris et al.[45] also showed an increased SMR. Baris reported an SMR of 168 (95% CI: 117-240) in Philadelphia fire fighters. In this study, the fire fighters were stratified by exposure according to the number of runs made. Fire fighters in the low exposure group (<3,323 runs) had a significantly increased SMR of 193 (95% CI: 129-291) for colon cancer while fire fighters in the medium exposure group (≥ 3,323 & < 5,099 runs) had a significantly elevated SMR of 222 (95% CI: 136-362)[45]. Fire fighters in the high exposure group (≥ 5,099 runs) had a non-significantly elevated SMR of 122 (95% CI: 64-235). A significant pooled estimate of 116 (95% CI: 106-126) was obtained when all of the studies in the review were considered.

***Esophageal*:** Beaumont et al. reported a significantly elevated SMR of esophageal cancer in a group of 3,066 fire fighters from San Francisco [53]. Beaumont and colleagues stratified the study population by duration of employment and time since first employment but neither grouping produced significantly elevated results [53]. A slightly elevated SMR for esophageal cancer (101, 95% CI: 80-128) was obtained when risk estimates from all studies reviewed were pooled.

***Hematopoietic/Lymphathic*:** A significantly elevated proportionate mortality ratio (PMR) of cancer in the lymphatic system (PMR = 130, 95% CI: 111-151) was found by Burnett et al. in a study of white male fire fighters from 27 different states [60]. Demers et al. reported a significantly elevated SMR of hematopoetic and lymphatic cancers in fire fighters with more than 30 years of exposed employment (SMR= 205, 95% CI: 110-360) and in fire fighters with more than 30 years since first employment (SMR= 148, 95% CI: 100-220) [46]. A significantly elevated pooled estimate of 114 (95% CI: 101-129) was obtained when risk estimates from all studies reporting hematopoietic/lymphatic cancers were combined.

Some studies further divided the hematopoietic/lymphatic cancer category into leukemia and non-Hodgkin's lymphoma. A nonsignificantly increased risk estimate of 112 (95% CI: 96-131) was obtained when studies reporting leukemia were pooled. For non-Hodgkin's lymphoma, a significantly elevated pooled estimate of 136 (95% CI: 118-158) was obtained in this systematic review.

***Kidney*:** Risk estimates for kidney cancer range from 27 (95% CI: 3-97) [46] to 414 (95% CI: 166-853) [52]. The latter risk estimate was reported by Guidotti et al. in the study of 3,328 fire fighters from Canada [52]. The study also reported a significantly elevated SMR of 2,130 ($p < .01$) in fire fighters with 40-49 years of latency and a significantly increased SMR of 2,550 ($p < .01$) in fire fighters with 40-49 years of latency with an exposure index great than or equal to 10. Baris et al. also found a significantly elevated SMR of kidney cancer (SMR= 220, 95% CI: 118-408) among 7,789 fire fighters from Philadelphia employed more than 20 years [45]. When risk estimates were pooled, a significantly elevated estimate of 144 (95% CI: 123-170) was obtained.

***Larynx*:** An elevated, SMR of laryngeal cancer (111, 95% CI: 80-155) was found when risk estimates from several studies were pooled. SMRs ranged from 37 (95% CI: 1-206) [1] to 238 (95% CI: 126-409) [50].

***Liver*:** Liver cancer SMRs in studies of fire fighters and cancer range from 82 (95% CI: 41-164) (Baris) [45] to 191 (95% CI: 87-363) (Beaumont) [53], though no reported risk estimates were significant. An estimate of 121 (95% CI: 95-154) was obtained when SMRs were pooled.

***Respiratory/ Lung Cancer*:** Pooled respiratory and lung cancer SMRs in fire fighters were shown to be similar to SMRs in the general population (104, 95% CI: 99-109). Beaumont et

al. stratified lung cancer risk estimates in fire fighters by time since first employment and length of employment; neither produced elevated estimates [53].

***Pancreas*:** Pancreatic cancer SMRs ranged from 38 (95% CI: 4-136) [51] to 200 (95% CI: 90-460) [55]. An elevated pooled estimate of 116 (95% CI: 100-134) was obtained when studies reporting pancreatic cancer were combined. Stratification of estimates by time since first employment and length of employment for 3,066 San Francisco fire fighters resulted in nonsignificantly elevated estimates [53].

***Prostate*:** Studies of cancer in fire fighters report prostate cancer SMRs from 38 (95% CI: 16-75) [53] to 261 (95% CI: 138-497) [58]. In a study of 2,447 fire fighters from Seattle and Tacoma, fire fighters with 20-29 years of experiences and fire fighters with 30 or more years since first employment had significantly higher SMRs of prostate cancer (150 and 130, respectively) than the local county population [46]. Pooling of the risk estimates from cancer studies in fire fighters resulted in a significant estimate of 127 (95% CI: 116-139).

***Skin Cancer*:** A significant pooled estimate of 149 (95% CI: 125-177) was obtained when risk estimates for skin cancer in fire fighters were pooled. Reported estimates for skin cancer ranged from 73 (95% CI: 9-263) [1] to 292 (95% CI: 170-503) [54]. Baris et al. reported an SMR of 310 (95% CI: 129-746) in a study of 7,789 fire fighters from Philadelphia with medium exposure (greater than 3,323 and less than 5,099 runs) [45].

***Stomach Cancer*:** Tornling et al. reported an elevated, though not significant, SMR of 121 (95% CI: 62-211) for stomach cancer in fire fighters from Stockholm [59]. The study did report significantly elevated SMRs for fire fighters with increased exposure. Fire fighters with greater than 30 years of employment and fire fighters exposed to more than 1,000 fires had

SMRs of 289 (95% CI: 149-505) and 264 (95% CI: 136-461), respectively. With pooling of the risk, a nonsignificant SMR of 110 (95% CI: 95-129) was obtained.

***Rectal Cancer*:** A pooled estimate of 136 (95% CI: 117-157) was obtained when studies reporting rectal cancer in fire fighters were combined. Beaumont et al. [53] stratified the analysis by time since employment and length of employment; the estimates were elevated but not significantly.

***Buccal Cavity/Pharynx*:** Rates of buccal cavity and pharyngeal cancer were elevated, but not significant in cancer studies of fire fighters. A nonsignificant estimate of 122 (95% CI: 92-161) was obtained when estimates were pooled.

***Testicular Cancer*:** Testicular cancer SMRs were reported in two studies. Pooling these studies yielded a significantly elevated pooled SMR of 300 (95% CI: 102-890).

Summary: After pooling data across studies, modestly elevated and statistically significant risks of cancer in fire fighters were obtained for the following cancer categories: all cancer combined and, bladder, brain, colon, hematopoietic/lymphatic, kidney, pancreas, prostate, skin, rectal, and testicular cancers (Table 3). Non-significant elevations were found for cancers of the larynx, liver, respiratory system, stomach, and buccal cavity/ pharynx. The limited data available indicate that fire fighters with greater exposure to fires (increase number of runs, greater number of years served as a fire fighter) have higher risks of cancer.

Case-Control Studies of Occupation and Brain Cancer

An epidemiologic method often used to study exposures and outcomes is the case-control study. In a case-control study, people who already have the outcome of interest (cases) and people without the outcome of interest (controls) are asked questions to assess common

exposures that they might have had. Investigators use odds ratios to describe the level of risk estimates from an exposure in this type of study. An odds ratio is calculated by measuring the proportion of the cases that were exposed and the proportion of the controls that were exposed [42]. Figure 3 shows how an odds ratio is calculated.

A number of studies have assessed associations between specific occupations and brain cancer (Table 4) [54; 55; 61-75]. Many of these studies have reported risk estimates for people working in the agricultural, rubber, and petroleum industries [61;63;68;71;73;75]. The evidence on occupational exposure in fire fighters and brain cancer is not so abundant. Brownson and colleagues investigated the risks of brain cancer and employment history in a case-control study of 312 cases and 1,248 cancer controls [61]. They reported an elevated, but not statistically significant, risk estimate of 2.00 (95% CI: 0.40-9.60) for fire fighters. Other studies have reported elevated odds ratios ranging from 1.00-6.90 in fire fighters. The only statistically significant estimate was from a study looking at race-specific cancer mortality in US fire fighters [55]. The authors found that African-American fire fighters had a statistically significant elevated odds ratio of 6.9 (95% CI: 3.0-16.0).

PCB Literature Review

A comprehensive literature search was conducted of English-language journals using the MEDLINE database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed , January 1966- September 2004) for articles pertinent to PCBs and cancer, the half-life of PCBs, and PCB biomarker studies. Reference lists from identified articles were also reviewed to obtain additional citations.

For this search, the terms and the numbers of titles returned were:

PCBs	N= 8586
PCB and epidemiology	N= 179
Occupational exposure and PCB and Cancer	N= 21
Occupational exposure and PCB and Mortality	N= 7
PCB and half life	N= 60
PCB elimination	N= 81
PCB and adipose tissue sampling	N= 14
PCB biomarkers	N= 20

We reviewed 382 abstracts (60+81+14+20+179+21+7) for relevance to the subject matter. Inclusion criteria for this search consist of reporting:

- Concentration levels of PCBs for populations exposed occupationally
- Half-life estimates for various congeners of PCBs
- Listing specific biomarkers for detecting exposure to PCBs.

Articles were excluded from review if they did not meet any of the search criteria, were not written in English, or were duplicative publications of each other. After these exclusions, a total of 23 articles were included in the evidence tables. In all iterations of the search, references from full text articles read were reviewed for additional citations.

One reviewer (NB) assessed 382 titles and abstracts for relevance to the topic at hand. Information from the 23 articles was extracted; variables extracted from relevant articles include authors' names, year of publication, population studied, study design, risk estimate, PCB congener, half-life estimation, confidence interval or p-value, cancer site, exposure, and occupation. These variables were used to create evidence tables.

Epidemiologic Studies

The carcinogenicity of PCBs has been investigated in occupational studies of capacitor workers and in case-control studies of the general population (Table 2). Significantly elevated rates of skin, gastrointestinal, hematological, and pancreatic malignancies, and melanoma

have been reported in capacitor and transformer workers [32;38;76;77], although findings are not consistent across the studies, perhaps due to variations in length of exposure and the PCB congeners present. In a retrospective cohort study of 3,588 capacitor manufacturing workers, Sinks et al. reported a statistically significant elevated SMR of skin cancer (SMR= 410, 95% CI: 180-800) [31] . In a study of 2,100 male and female capacitor production workers, Bertazzi et al. reported SMRs of 183 (95% CI: 104-300) and of 274 (95% CI: 112-572) for malignant tumors and cancer of the gastrointestinal tract in males, respectively [32]. In females, Bertazzi et al. reported SMRs of 226 (95% CI: 123-385) and 377 (95% CI: 115-877) for malignant tumors and hematologic neoplasms, respectively [32].

Biomarker Studies

Levels of PCBs can be measured in blood and adipose tissue. Studies of adipose tissue samples have shown elevated levels of PCBs in workers occupationally exposed to PCBs (Table 5) [11;31;32;78-86]. Transformer repair workers had a mean adipose PCB level of 2.1 ppb, while comparison workers had mean concentrations of 0.6 ppb [79]. A study of serum PCB levels in workers after a transformer fire reported mean levels of 2.92 ppb ± 1.96 for 58 out of the 60 fire fighters. Twenty fire fighters had PCB levels greater than 1.8 ppb and five fire fighters had PCB levels above 6 ppb. The mean serum level for individuals who do not have diets high in fish from PCB contaminated waters is between 0.9-1.5 ppb [27].

Estimates of half-lives of PCBs in occupationally exposed populations vary according to the congener present (Table 1). Half-lives of 6 months to 7 years have been measured in occupationally exposed populations [28;29].

Combustion of PCBs can lead to the formation of furans and dioxins [87], further complicating the evaluation of the health effects of PCBs. There over 200 congeners of furans

and dioxins associated with PCB combustion. Dioxins have been classified by IARC as either Group 1 (carcinogenic to humans) or Group 3 (not classifiable as carcinogenic to humans), depending on the number and position of substituted chlorines present [22]. The Group 1 classification includes 2,3,7,8-tetrachlorodibenzo-*para*-dioxin while the Group 3 classification includes polychlorinated dibenzo-*para*-dioxins (other than 2,3,7,8-tetrachlorodibenzo-*para*-dioxin) and dibenzo-*para*-dioxin.

REPORTS FROM ANNE ARUNDEL COUNTY FIRE FIGHTERS

Information about occupational exposures and cancers or other health concerns among fire fighters was obtained through a questionnaire administered via telephone. The Johns Hopkins team collaborated with fire fighter union representatives (Anne Arundel County Professional Fire fighters Local 1563, Anne Arundel County Retired Fire fighters Association, Anne Arundel Volunteer Fire fighters Association, and Professional Fire fighters of Maryland) to inform fire fighters and/or their families to contact the Hopkins investigators to complete the questionnaire (Appendix E). Information was disseminated by the union representatives in emails and at various organizational meetings held by the union groups. Information was further relayed at the open forum meeting held at Old Mill High School in Anne Arundel County on October 18, 2004. Fire fighters participated in dissemination of information by alerting their friends and colleagues to the effort by the Johns Hopkins team to collect occupational and cancer history of exposed individuals. Individuals interested in completing the questionnaire called a Johns Hopkins investigator and answered questions posed by the investigator. Information collected fell into three categories: demographic, occupational, and medical. Responses were collected from November, 2004 to May, 2005.

Seventeen fire fighters (all male) reported a diagnosis of at least one form of cancer. Respondents ranged in age from approximately 30 to 70 years. Fire fighters who were fully vested in the pension system had an average of 27 years of firefighting experiences before retirement. Primary cancer sites reported include bladder, brain, colon, leukemia or lymphoma (Hodgkin's or non-Hodgkin's), lung, prostate, and skin. Skin cancer was the most commonly reported cancer, representing 47% of the cancers. Excluding skin cancer, brain cancer (n=2) and leukemia/lymphoma (n=3) were the most common forms of cancer at 22% and 33%, respectively.

ANNE ARUNDEL COUNTY CANCER DATA

Another approach to evaluate the impact of the exposures to fire fighters on cancer incidence is to analyze data on cancer rates for Anne Arundel County residents, particularly males. This approach is quite insensitive but might detect any unusual patterns of cancer incidence, particularly for relatively uncommon cancers and within particular age groups.

Consequently, we obtained data on the number of cancer cases by site for the entire Anne Arundel County population from the Maryland Cancer Registry. The rate of new cancer cases in Anne Arundel County was compared with data for the entire state of Maryland over strata of age and sex. Table 6 lists standardized incidence ratios (SIR) comparing rates of cancer in Anne Arundel County with rates of cancer in Maryland (Appendix F contains data for all sites). A standardized incidence ratio (SIR) greater than 100 represents a greater than expected rate of new cases of cancer in Anne Arundel County. The overall SIRs for all sites, melanoma, and skin (not basal or squamous) were significantly elevated for Anne Arundel County. The overall SIRs for bladder cancer in males and for cervical and digestive cancers in females were also elevated and statistically significant. People from Anne Arundel County

had a greater than expected number of cases of these cancers than the general Maryland population.

SUMMARY AND SYNTHESIS

Over the course of the 10 months of this study, we have gathered a diverse body of evidence relevant to concerns about a cluster of cancer cases among Anne Arundel County fire fighters that initiated this project. Investigation of cancer clusters is known to be difficult, often leading to findings that frustrate both public health authorities and those who are concerned about cancer risk [88;89]. On one hand, the finding of a cancer cluster may signal the consequences of the shared exposure of a group of people to one or multiple carcinogens; on the other hand, the occurrence of a cluster may reflect the play of chance, as thousands of cases of cancer are diagnosed every year, and some cases would be seemingly linked by occurring among people of similar demographic characteristics, people who have lived near one another, or people who had similar jobs. Nonetheless, cancer clusters are often investigated by public health authorities to make certain that a causal factor is not overlooked and to provide information on possible explanations to those affected and concerned about their risk. Cluster investigations are often limited in their scientific scope by the number of cases in the cluster, the amount of information available, and the resources provided for the investigation.

Fire fighters have exposures to carcinogens and toxins. Their risk for cancer and other diseases has been investigated by epidemiologists with the finding of increased risk for some sites. In our literature review, risk of death from brain cancer was increased by 30 percent in fire fighters compared to the general population. Risks for death from cancers of several other sites were also elevated (Table 3).

In the case of the Anne Arundel County fire fighters, the accounts of the training fires and the use of PCB-contaminated oil establish that participants in the training exercise had exposure to PCBs, classified as a probable human carcinogen, through the inhalation and dermal routes, as well as to toxic compounds that would have been generated by the fires. The scientific literature indicates that another group of carcinogens, polychlorinated dibenzo-*p*-dioxins, are formed by combustion of PCBs [18;19] and the fire fighters would have inhaled these carcinogens as well. The information reported by the Anne Arundel County Fire Department on the circumstances of the fires and the descriptions of the fire fighters are sufficient to establish that the training fires were associated with exposures to carcinogens.

However, the doses of PCBs and combustion by-products received, which would be predictive of any resulting increase in risk, cannot be readily reconstructed. The doses received by the fire fighters and instructors would have depended on the number of training fires with which they had contact and the circumstances of each particular fire. The levels of PCBs and byproducts in individual fire fighters would also be expected to vary with characteristics of individuals that determine uptake, metabolism, distribution, and excretion of these compounds. There is likely substantial variation among individuals in doses as a result. Retrospectively, no strategy is readily available to reconstruct doses, as the literature suggests too much variability of tissue levels, and no measurements of concentration were taken at the time. Additionally, substantial time has passed since the exposures to the training fires so that tissue and blood concentrations would be expected to have dropped substantially. One strategy would be to reconstruct the circumstances of the fires and then to take detailed measurements, but any extrapolation of the resulting data would be highly uncertain. It is thus difficult for us to judge whether the doses received, on average, would have reached a range at which increased cancer risk would be anticipated. The dose-response relationships

for PCBs and combustion by-products are not characterized with sufficient certainty for such judgments about risk.

Neither the information about the cluster nor the cancer incidence data for Anne Arundel County is informative about the potential risks for participants in the training fires. The information on the cluster, particularly as brain cancer is uncommon, raises concern, and our review of the studies of the fire fighters found an indication of increased risk. Because we have only the count of the number of brain cancer cases, we cannot calculate the number expected without carrying out a formal epidemiological study. A specific linkage of brain cancer to PCB exposure or to compounds generated by their combustion has not been demonstrated. However, this lack of evidence does not establish that there is *no risk*, however, and further research on risks for cancer and other diseases among fire fighters is needed. Below, we offer recommendations.

RECOMMENDATIONS

1. A strategy is needed for communicating the findings of this report to the fire fighters in Anne Arundel County, as well as those from other jurisdictions who participated in fires at the Academy during the years that the PCB-contaminated oil was in use for training fires. We will work with DHMH, the unions, and the Fire Department to assure that the findings are communicated with opportunity for questions, clarification, and amplification.
2. One approach to better understand the doses of PCBs that may have been associated with the fires is to measure levels of PCBs in either blood or adipose tissue. These measurements are not readily made and are costly. Our review of the literature

indicates that measurements of biomarker levels would not be useful. Confirmation of this opinion might be sought from someone with specific expertise in this area.

3. The US Preventive Services Task Force and the American Cancer Society periodically make recommendations for routine cancer screenings. Such recommendations should be followed to enhance the possibility of early detection of cancers for which routine screening is recommended. At present, screening is not recommended for either lung cancer or brain cancer, two sites of potential concern for the fire fighters.

4. With the scope of funding available and the limited time of this project, a formal epidemiological study of Anne Arundel County fire fighters could not be undertaken. One approach that could be used for that purpose would use the retrospective cohort design. With this design, an attempt would be made to identify all Anne Arundel County fire fighters who worked during a time when exposure to the training fires with PCB-containing oil took place. Record linkage and other follow-up methods would then be used to determine who developed cancer so that the rate of cancer development in the cohort could be compared to that in the general population or another worker group. This study might be limited by the number of potential participants; on the other hand, it would provide surveillance for risks in this population and position the Fire Department and the State of Maryland to respond to concerns about occurrence of cancer or other diseases with actual data.

Records could be used to establish a cohort of fire fighters who were employed in the era when the training facility was in use. We learned that the exposed population extends beyond the Anne Arundel County fire fighters. Occurrence of cancer could then be documented by linkage to the Maryland Cancer Registry and other registries, as well as to the National Health Index. The population available for

study numbers under 1,000, so that the small numbers of cancers anticipated might leave uncertainty as to increased risk, unless there was an unusually strong risk detected. Such a study, however, would be the most direct approach to gain evidence relevant to the cancer risks from using the PCB contaminated fuel. The results might be inconclusive because of the numbers of fire fighters who could be studied; however, no other approach can add further, useful evidence to the study that we have carried out.

5. Our systematic review of the evidence on cancer risks among fire fighters yielded a remarkably limited body of evidence. The number of studies is not large and the populations investigated are small in most studies. Example calculations of sample size (Appendix G) are provided to indicate number of participants needed for an informative study. We suggest that consideration be given to the development of a larger study of disease risks among fire fighters, drawing on contemporary epidemiological approaches. Fire fighters continue to face unavoidable, hazardous exposures on a routine basis and the exposures received change as materials change. Ongoing surveillance strategies, involving biomonitoring and tracking of illness and mortality, should be set in place.

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cancer registry data were provided by Afaq Ahmad of the Maryland Cancer Registry. This project was approved by the Johns Hopkins Bloomberg School of Public Health Committee on Human Research and the Maryland Department of Health and Mental Hygiene Institutional Review Board. We recognize the bravery of the fire fighters and the extent of the hazards that they face regularly.

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