Firefighters, Cancer, and Carcinogens

Results of Literature Searches, a Presentation at the SOT Annual Meeting in San Antonio, Texas (March 2018) and Review of Documents Supplied by the Fire Smoke Coalition, Indianapolis, Indiana, USA

Alan H. Hall, M.D.
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1. **Results of Literature Searches:**
   2 Literature Searches in NLM's PubMed Database

   - **Search Terms: "Firefighters Cancer"**
   - **Search Terms: "Fire Smoke Carcinogens"**

   a. **Retrieved Free Full Text Pertinent Articles**

      Baxter CS, Hoffman JD, Knipp MJ, Reponen T, Haynes EN. Exposure of firefighters to particulates and polycyclic aromatic hydrocarbons. J Occup Environ Hyg 2014; 11(7):D85-D91; doi: 10.1080/15459624.2014.80286.

      PAHs have been detected a fire scenes and in fire station rest areas and kitchens (adjoining equipment bays) where firefighters spend much of each shift.

      Aim: An academic-community partnership was formed with the Cincinnati Fire Department to study the airborne and dermal PAH exposures of active firefighters. PAHs were measured in air for number and mass concentrations of particulates (submicron, 0.02-1μm; PM 2.5 [2.5 μm and less]) during overhaul events in two fire stations and in a University of Cincinnati administrative facility for comparison. Firefighters often remove SCBA during the overhaul phase of firefighting. Face and neck wipes were also obtained at a domestic fire scene.

Overhaul PAH airborne levels had higher mean concentrations of submicron and PM 2.5 particles than did samples obtained mainly in equipment bays and kitchens of fire stations.

Of 17 analyzed PAHS, only naphthalene and acenaphthylene were generally detectable (naphthylene in 7 of 8 overhaul activities and in 2 of 3 fire station equipment bays and kitchens – none was detected in the comparison facility).

A greater number of PAHs were found on firefighter face and neck wipe samples, several of which have known carcinogenic activity, (i.e., benzofluoranthracene) which was also found in overhaul air samples.

While the concentrations of PAHs were generally low for naphthalene and all other individual PAHs, the potential for exposure to multiple such chemicals suggest that further study is warranted. These authors recommended that SCBA and skin protection be worn during overhaul activities.

Dahm MM, Bertke S, Allee S, Daniels RD. Creation of a retrospective job-exposure matrix using surrogate measures of exposure for a cohort of US career firefighters from San Francisco, Chicago, and Philadelphia. Occup Environ Med 2015; 72(9):670-677; doi: 10.1136/oemed-2014-102790.

Aim: To develop a cohort-specific job exposure matrix (JEM) to be used in a cancer study of career firefighters from the Chicago, Philadelphia, and San Francisco Fire Departments employing surrogate metrics of exposure.

The cohort was comprised of all male firefighters employed at the 3 departments for one or more years between 1950 and 2009. The average duration of employment for all 3 departments was 20.7 years. The average cumulative duration of exposure was 15.7 years.

Fire Department work history records together with data on fire runs and hours-on-scene were obtained from 1950-2009 and

coded into separate databases to create a job exposure matrix using surrogate metrics for estimating firefighters' exposure to fire combustion by-products. These metrics were:

- Duration of Exposure: Cumulative time with a standardized exposed job title and assignment
- Fire-runs: Cumulative events of potential fire exposure
- Time at Fire: Cumulative hours of potential fire exposure

The initial JEM consisted of 2,298 unique job titles together with 16,174 fire apparatus assignments from 3 departments, which were then collapsed into15 standardized job titles and 15 standardized job assignments.

Correlations were found between fire-runs and time at fires (Pearson coefficient = 0.92), duration of exposure and time at fires (Pearson coefficient = 0.85), and duration of exposure and fire-runs (Pearson co-efficient = 0.82). While duration of employment has traditionally been used as an exposure surrogate in many previous epidemiological studies, total misclassification rate varied from 16-30% when compared with using the duration of exposure surrogate metric.

Daniels RD, Kubale TL, Yiin JH, Dahm MM, Hales TR, Baris D, Zahm SH, Beaumont JJ, Waters KM, Pinkerton LE. Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). Occup Environ Med 2014; 71(6):388-397; doi: 10.1136/oemed-2013-101662.

Aim: To determine the patterns of cancer mortality and cancer incidence in a pooled cohort of 29,993 US career firefighters employed since 1950 and followed through 2009.

Cancer incidence and mortality were evaluated with the US reference population by life table methods. The SMRs (Standardized Mortality Ratios) and SIRs (Standard Incidence Ratios) were determined for 92 causes of death and 41 cancer

incidence groupings. The data analysis focused on 15 *a priori* outcomes and sensitivity analyses were conducted to assess significant bias potential.

There were 22,993 firefighters in the cohort who were employed for at least one day in the San Francisco, Chicago, or Philadelphia Fire Departments.

Total person-years-at-risk were 858,938 (mortality) and 403,152 (cancer incidence). Excess cancer mortality was found among firefighters (SMR = 1.14; 95% CI = 1.10-1.18; n= 3,285). Excess cancer incidence was also found among firefighters (SIR = 109; 95% CI= 1.06-1.12; n = 4,461). Excess cancer incidence was mainly comprised of digestive tract cancers (SMR = 1.26; 95% CI = 1.18-1.34; SIR = 1.17; 95% CI = 1.10-1.25; n= 928), and respiratory tract cancers (SMR = 1.10; 95% CI = 1.04-1.17; SIR= 1.16; 95% CI = 1.08-1.24; n = 813).

As in previous studies, there were modest increases in certain solid cancers, but no increase in lymphatic or hematopoietic cancers. Excess mesotheliomas were found, however (SMR = 2.00; 95% CI = 1.03-3.49; SIR = 2.29; 95% CI = 1.60-3.19; n = 93).

Daniels RD, Bertke S, Dahm MM, Yiin JH, Kubale TL, Hales TR, Baris D, Zahm SH, Beaumont JJ, Waters KM, Pinkerton LE. Exposure-response relationships for select cancer and non-cancer health outcomes in a cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). Occup Environ Med 2014; 71(6):388-397; doi: 10.1136/oemed-2013-2013-101662.

Aim: To examine exposure-response relationships between surrogate exposure metrics and selected outcomes amongst the cohort of previously-studied US career firefighters (see Daniels RD et al, 2014 above).

Eight cancer outcomes were examined using conditional logistic regression. Incidence density sampling was used to match each case to 200 attained-age controls. Examined surrogate exposure metrics were: Exposed days (days accrued in firefighting assignments), Fire runs (run totals), Fire hours (run times). Piecewise constant models were used to examine risk differences by: time since exposure, age at exposure, and calendar period.

Selected cancer outcomes studied were:

- All cancers
- Bladder cancers
- Colorectal cancers
- Esophageal cancers
- Lung cancers
- Prostate cancers
- Leukemia
- Non-Hodgkin's lymphoma

Among the total 19,309 male career firefighters in the study cohort, there were 1,333 cancer deaths and 2,609 cancer incidence cases. Significant positive associations were found between fire-hours (run times) and both lung cancer mortality and incidence. There was a similar relationship between fire runs (run totals) and leukemia mortality. Both lung cancer and leukemia mortality risks were modestly increased with firefighter exposures.

There was little evidence of an exposure-response relationship for all cancers combined or for most separate malignancies with the exceptions of cancers of the lung, colorectal sites, prostate, and leukemia.

Demers PA, Heyer NJ, Rosenstock L. Mortality among firefighters from three northwestern United States cities. Br J Ind Med 1992; 49:664-670.

Aim: Explore whether firefighters exposed to fire smoke have an increased risk of cancer and other diseases in a retrospective cohort study.

Cancer mortality among a cohort of 4,566 male firefighters from the cities of Seattle and Tacoma, Washington, and Portland, Oregon employed for at least 1 year was compared with the US national mortalities and those of police officers from the same cities. Years of active service was used as a surrogate metric for fire smoke exposure. 1,169 deaths occurred between 1945 and 1989, and 1,162 Death Certificates (99%) were obtained. Complete follow-up was achieved for 98% of the firefighter cohort.

No overall increased risk of cancer deaths was found. However, there were excess death from brain cancer (SMR = 2.09; 95% CI = 1.3-3.2) and lymphatic and hematopoietic cancers (SMR = 1.31; 95% CI = 0.9-1.8). Firefighters <40 years of age had an excess risk of brain cancer (SMR = 1.45; 95% CI = 1.2-8.7). Firefighters with at least 30 years of service had an excess risk of lymphatic and hematopoietic cancers (SMR = 2.05; 95% CI = 1.0-5.4), which was greater than the risk for all firefighters in the cohort.

Brain tumors listed on the death certificates were:

- Glioblastoma multiforme (7 cases)
- Astrocytoma (3 cases)
- Other gliomas (3 cases)
- Other or unspecified brain tumors (5 cases)
- Unspecified brain tumors (4 cases)

Smaller excesses of lymphatic and hematopoietic cancers were found amongst all firefighters (SMR = 1.31; 95% CI = 0.92-1.81) and prostate cancers (SMR = 1.34; 95% CI = 1.91).

Relative to the police comparison group, firefighters had an increased risk of multiple myeloma (SMR = 1.91; 95% CI = 0.4-8.4).

Amongst those firefighters with at least 30 years of service, the following excess risks were found:

- Brain tumors (SMR = 2.63)
- Lymphatic and hematopoietic malignancies (SMR =1.48)
- Prostate cancer (SMR = 1.42)

Edelman P, Osterloh J, Pirkle J, Caudil SP, Grainger J, Jones R, Blount B, Calafat A, Turner W, Feldman D, Baron S, Bernard B, Lushniak BD, Kelly K, Prezant D. Biomonitoring of chemical exposures among New York City firefighters responding to the World Trade Center fire and collapse. Environ Health Perspect 2003; 111(16):1906-1911.

Aim: To use biological monitoring in blood and urine of firefighters responding to the September 11, 2001 collapse of the World Trade Center (WTC) in New York compared to control firefighters who did not respond to the WTC disaster.

Blood and urine specimens obtained from 321 firefighters who responded to the WTC disaster and 47control firefighters were analyzed for 110 potential fire-related chemicals. Samples were obtained 3 weeks after the disaster when fires were still burning.

For those chemicals with reference or background ranges available, most chemical concentrations were low and not outside these ranges. Compared to controls, WTC responders had significantly increased adjusted geometric means for 6/110 chemicals and significantly increased detection rates for 3 others. Arrival time at the WTC site was a significant predictor for 4 chemicals. Firefighters in Special Operations Command (SOC) (n=95) compared to other WTC responders (n=226) had differences is either concentrations or detection rates for 14/110

chemicals. SOC firefighters had the same differences compared to controls for these same chemicals.

Analyzed chemicals included:

- VOCs (Volatile Organic Compounds)
- PAHs
- Dioxins
- Furans
- PCBs
- Metals (Lead, Antimony, Cadmium, Uranium)

Those chemicals with increased Adjusted Geometric Mean concentrations (ANCOVA analysis) were:

- 1-Hydroxypyrene*
- 1-Hydroxyphenanthrene
- 2-Hydroxyphenanthrene
- 3-Hydroxyphenanthrene
- 1,2,3,4,6,7,8-Heptachlorodibenzodioxin*
- 1,4-Dichlorobenzene
- *meta/para*-Xylenes*
- Methyl *tert* butyl ether
- Lead*
- Antimony*
- Cadmium
- Uranium*

*For all WTC-exposed firefighters, significantly different from controls

Although some of the 110 chemicals analyzed were statistically significantly different, the differences were generally small. Statistically significant increases in concentrations, however, were generally low compared to the general US population, reference values, and established workplace threshold levels.

Gomes J, Al Zayadi A, Guzman A. Occupational and environmental risk factors of adult primary brain cancers: A systematic review. IJOEM 2011; 2(2):82-111.

The incidence of neoplasms of the brain in industrialized countries has been increasing progressively in recent years.

While risk factors have been identified such as genetic, ethnic, and age-based, there are potential environmental and occupational factors, one of which is the profession of firefighting.

Primary malignant brain cancers seem to be more prevalent in industrialized countries with access to advanced medical care (and diagnostics), but the actual reason(s) for this prevalence is/are not actually known.

Workers in professions where the potential for high levels of chemical exposures exists include firefighters.

Approximately 90% of malignant CNS neoplasms are gliomas, and approximately 94% of these occur in the brain. The authors concentrated on intracranial malignant gliomas, astrocytomas, and meningiomas, for which an occupational risk factor includes the profession of firefighter, who also have a somewhat higher risk compared to other professions.

Firefighters may have a higher risk for developing such neoplasms because of exposure to such chemicals as:

- Vinyl chloride
- Benzene
- n-Hexane
- PAHs
- PCBs
- N-nitroso compounds
- Lead
- Arsenic

- Mercury

Hansen ES. A cohort study on the mortality of firefighters. Br J Ind Med 1990; 47:805-809.

Aim: To evaluate the effects of exposure to combustion effluents on firefighters' chronic health.

The Danish firefighter study cohort was identified from a nationwide census done in 1970. Self-reported occupations of firefighter or fireman (public employees) made up the cohort. A comparison cohort of civil servants and salaried employees in physically demanding jobs was similarly identified.

Overall mortality of firefighters was not different from that of the comparison cohort.

After a five-year latency period, excess mortality from cancer was found in firefighters (SMR=173; 95% CI=104-270) aged 30-74 years. A significant increased excess of lung cancer was found in those firefighters aged 60-74 years (SMR=317; 95% CI=117-691) and a significant non-pulmonary cancer excess was found for those firefighters aged 30-49 years (SMR=575; 95% CI=187-1341).

The excess in non-pulmonary cancers was due to 5 deaths: stomach cancer (1); rectal cancer (2); pancreatic cancer (1); "other localization" (1).

Hong YC, Park H-Y, Ha E-H. Influence of genetic susceptibility on the urinary excretion of 8-hydroxydeoxyguanosine of firefighters. Occup Environ Med 2000; 57:370-375.

Aim: To evaluate the genetic susceptibility of the urinary excretion of 8-hydroxydeoxyguanosine (8-OH-dG) amongst firefighters.

Oxidative DNA damage has been implicated in development of cancer and can be evaluated from the urinary excretion of 8-OH-dG.

Of 78firefighters evaluated, 53 (68%) had been exposed to fires within 5 days of sampling and 25 (32%) had not.

Urinary 8-OH-dG was measured by ELISA and the distribution of genotypes of CYP1A1, CYP2E2, GSTM1, and GSTT1 was measured by polymerase chain reaction (PCR). Homozygous wild type frequencies were:

Genotype	**Frequency**
CYP1A1 *msp*I	31.5%
CYP1A1 ileval	56.2%
CYP2E2	60.3%
GSTM1	50.7%
GSTT1	53.4%

Geometric means of 8-OH-dG were 14.1 ng/mg creatinine in more active firefighters and 12.3 ng/mg creatinine in less active firefighters. Significant increases in 8-OH-dG excretion were associated with tobacco smoking.

Age, body mass, and firefighting activity were not significant predictive factors for urinary 8-OH-dG excretion.

Both tobacco smoking and the CYP2E2 gene polymorphism may be important factors for carcinogenesis amongst firefighters, and the GSST1 positive genotype may be a genetic susceptibility factor in firefighters regularly exposed to various chemical carcinogens.

Jacobson-Kram D, Albertini RJ, Branda RF, Falta MT, Iype PT, Kolodner K, Liou S-H, McDiarmid MA, Morris M, Nicklas JA, O'Neill JP, Poirier MC, Putman D, Strickland PT, Williams JR, Xiao S. Measurement of chromosomal aberrations, sister chromatid exchanges, hprt mutations, and DNA adducts in peripheral lymphocytes of human populations at increased risk for cancer. Environ Health Perspect Suppl 1993; 101(suppl 3):121-125.

These authors used a multidisciplinary approach to measure various indicators of DNA damage in peripheral lymphocytes of human populations with potential increased risk of developing cancers. Sister chromatid exchanges (SCEs) and polycyclic aromatic hydrocarbon (PAH)-DNA adducts were evaluated in a group of firefighters.

Neither SCEs nor PAH-DNA adducts levels were elevated in the group of firefighters.

A group of 43 firefighters and 38 matched controls were evaluated for DNA damage that might have been linked with occupational exposures to carcinogenic combustion products during firefighting operations. Peripheral blood lymphocytes were assayed for: 1) baseline Sister Chromatid Exchanges (SCEs); 2) SCEs induction with mitomycin C; 3) PAH-DNA adduct levels.

Occupational exposures were determined from histories of firefighting activities.

Mean baseline SCEs were lower in 42/43 firefighters than in 38 controls. Susceptibility to mitomycin C SCEs induction was statistically significantly *decreased* in firefighters. Firefighting was not associated with a significant risk for PAH-DNA adducts or benzo[a]pyrene diol epoxide (BPDE)-DNA antigenicity as determined by ELISA analysis in the DNA of enucleated peripheral blood samples. No association was found between baseline SCEs frequency and the presence of PAH-DNA adducts.

Liou S-H, Jacobson-Kram D, Poirier MC, Mguyen D, Strickland PT, Tockman MS. Biological monitoring of fire fighters: Sister chromatid exchanges and polycyclic aromatic hydrocarbon-DNA adducts in peripheral blood cells. Cancer Research 1989; 49:4929-4935.

Aim: To test a cohort of firefighters and matched controls for DNA damage possibly related to occupational carcinogenic chemical exposures.

A cohort of 43 firefighters and matched controls were evaluated for DNA damage using peripheral blood lymphocytes evaluated for baseline sister chomatid exchanges (SCEs), SCE induction by *in vitro* challenge with the mutagen mitomycin C, and using nucleated peripheral blood cells, evaluating PAH-DNA adduct levels by assessing benzo(a)pyrene diol epoxide (BPDE)-DNA antigenicity.

White firefighters had a significantly *greater* risk for the presence of detectable BPDE-DNA antigenicity than white controls (Odds Ratio=3.4; 95% CI=1.08-10.5).

Tobacco smoking and consumption of char-broiled foods, *but not firefighting*, were associated with increased baseline SCEs. Sensitivity to mitomycin C-induced SCEs was similar in the firefighter and control groups.

Sensitivity to mitomycin C-induced SCEs was correlated with the number of fires fought in the previous 24 hours for individual firefighters.

Musk AW, Monson RR, Peters JM, Peters RK. Mortality among Boston firefighters, 1915-1975. Br J Ind Med 1978; 35:104-108.

Aim: To examine the mortality experience from 1915-1975 among all (n=5,655) Boston city male firefighters with 3 or more years of service.

Observed causes of death (from death certificates) of 2,470 deceased firefighters were compared to numbers expected for the male population of Massachusetts and of the US general population.

The SMR (Standardized Mortality Ratio) was 83 for neoplastic diseases (cancers). While excessive morbidity has been shown in firefighters, in this study there was not a strong correlation between firefighting as an occupation and case-specific mortality. No evidence of an increased number of deaths from cancer was found for the population as a whole, but small sub-populations with excess risk may exist. The following Table shows the expected cancer deaths and SMRs for the 5,655 firefighters:

Cancer Cause of Death	Observed	Expected*	Expected+	SMR
Digestive System	153	191.5	154.2	80
Respiratory System	70	79.6	75.2	88
Genitourinary System	64	69.6	64.1	92
Brain, Other CNS	8	7.8	7.1	103
Lymphatic and Hematopoietic	22	34.9	27.4	63
Other Cancers	50	43.9	48.4	114

*Compared to Massachusetts death rates for all males
+compared to US death rates for white males

Mortality was not related to age, year of entry into the fire service, or age at death.

Ouyang B, Baxter CS, Lam H-M, Yeramaneni S, Levin L, Haynes E, Ho S-M. Hypomethylation of *dual specificity phosphatase 22* promoter correlates with duration of service in firefighters and is inducible by low-dose benzo[a]pyrene. J Occup Environ Med 2012; 54(7):774-780; doi: 10.1097/JOM.ob013e3182526bc.

Aim: To examine the possibility of an association between PAH-induced epigenetic alterations and exposure in firefighters.

Promoter methylation was analyzed in 4 genes in blood DNA from 18 firefighters and 20 non-firefighter controls. Jurkat and NPrEC cells were treated with benzo(a)pyrene to ascertain the potential epigenetic effects of this agent.

Genes examined were: glutathione S-transferase (GSTP1), interferon-γ (IFN-γ), RAD21 homologue (S. pombe) (RAD21), and DUSP22.

Firefighters had a higher prevalence of *DUSP22* promoter hypomethylation in blood DNA (p=0.03) and the extent of this was correlated not with age, but with duration of firefighting service (p=0.04). Benzo(a)pyrene reduced both methlyation and increased gene expression of the same gene in both Jurkat and NPrEC cells.

Of note, while firefighters have sometimes been said to have an increased risk of prostate cancer, measured blood PSA (prostate specific antigen)blood concentrations were all within the normal range in firefighters in this study. (**Also NOTE**: PSA has become an unreliable test in recent years as it over-detects the risk of developing prostate cancer and has lead to a great deal of unnecessary additional non-invasive and invasive testing and unnecessary surgical intervention—it has generally been discredited.)

This study concluded that cumulative occupational exposure to combustion by-products (PAHs) can cause epigenetic changes in specific gene promoters.

Rothman N, Correr-Villasenor A, Ford DP, Poirier MC, Haas R, Hansen JA, O'Toole T, Strickland PT. Contribution of occupation and diet to white blood cell polycyclic aromatic hydrocarbon-DNA adducts in wildland firefighters. Cancer Epidemiology, Biomarkers & Prevention 1993; 2:341-347.

Aim: To investigate the potential association between occupational and dietary PAH exposures and formation of white blood cell (WBC) PAH-DNA adducts amongst a cohort of wildland firefighters.

White blood cells (WBCs) sampled from 47 California wildland firefighters had measured PAH-DNA adducts with an enzyme-linked immunosorbent assay using an antiserum elicited against benzo(a)pyrene modified DNA. Sampling periods for the 47 wildland firefighter were early and late in the 1988 forest firefighting season.

While PAH-DNA adduct levels *were not correlated* with hours of recent firefighting activity, they were correlated with the frequency of consuming charbroiled foodstuffs.

Tsai RJ, Luckhaupt SE, Schumacher P, Cress RD, Deapen DM, Calvert GM. Risk of cancer among firefighters in California, 1988-2007. Am J Ind Med 2015; 58(7):715-729; doi:10.1002/ajim.22466.

Aim: To perform a case-control study using the California Cancer Registry data from 1988-2007 to evaluate the risk of firefighters developing cancer, and stratified by race. This registry collects data on all cancers (excluding non-melanoma skin cancers and in-situ cervical cancers).

Previous studies of cancer risks among firefighters were performed before 1990 and may not reflect the inherent risks from newer types of building materials involved in fires, such as polyvinylidene fluoride and laminated veneer lumber. Such newer materials, when burning or smoldering, may expose firefighters to new potentially carcinogenic combustion products.

This study included only male firefighters aged 18-97 years. 3,966 male firefighters with cancer were identified. Firefighters had a significantly increased risk of malignant melanoma (OR=1.8; 95% CI=1.4-2.1), multiple myeloma (OR=1.4; 95% CI=1.0-1.8), acute myeloid leukemia (OR=1.4; 95% CI=1.0-2.0), cancers of the esophagus (OR=1.6; 95% CI=1.2-2.1), prostate (OR=1.5; 95% CI=1.3-1.7), brain (OR=1.5; 95% CI=1.2-2.0), and kidney (OR=1.3; 95% CI=1.0-1.6).

Of 32 examined cancers, 3 were significantly increased amongst all firefighters combined and in both race groups:

- Malignant melanoma
- Prostate cancer
- Brain cancer

Three cancers were increased amongst all firefighters and among white firefighters:

- Adenocarcinoma of the esophagus
- Non-specific, non-small cell lung cancer
- Acute myeloid leukemia

Three cancers were increased amongst all firefighters and among those of other race/ethnicity:

- Kidney cancer
- Multiple myeloma
- Overall leukemia

Six cancers were increased only among firefighters of other race/ethnicity:

- Tongue cancer
- Testicular cancer
- Bladder cancer
- Non-Hodgkins lymphoma
- Chronic lymphocytic leukemia
- Chronic myeloid leukemia

This study found increased cancer risks for firefighters consistent with previous studies. It also provided information on firefighters of races other than Caucasian.

Zeig-Owens R, Kablanian A, Webber MP, Liu Y, Mayerson E, Schwartz T, Jaber N, Kelly KJ, Prezant DJ. Agreement between self-reported and confirmed cancer diagnoses in New York City firefighters and EMS workers, 2001-2011. Public Health Reports 2016; 131:153-159.

As there may be delays in posting of cancer diagnoses to cancer registries, self-reported diagnoses may be valuable in assessing current cancer burdens in certain populations. Confirmation of cancer cases in state cancer registries are not considered complete until approximately 2.5 years after the year of diagnosis. Also, certain types of cancers such as hematological cancers are likely to de diagnosed in physicians' offices rather than hospitals, which may increase delays in reporting to state registries or even lack of reporting in some cases.

This study evaluated self-reported cancer diagnoses as compared to nine state cancer registries (Arizona, Connecticut, Florida, New Jersey, New York, North Carolina, Pennsylvania, South Carolina, Virginia) for 21,437 firefighters and emergency medical service workers from the Fire Department of the City of New York during the period of 10/02/2001 to 12/31/2011. The potential association between exposure at the world Trade

Center (WTC) disaster and other characteristics was also investigated.

Aim: Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated by comparing self-reported cancer diagnoses with those obtained from the cancer registries.

A questionnaire was administered and a self-reported diagnosis of cancer was determined by a positive answer to the question: "Has your doctor ever told you that you have or had cancer?"

During the study period, 890 persons (4.2%) self-reported one or more cancer diagnoses, while only 3.2% had at least one confirmed cancer diagnosis. For all cancers combined, the sensitivity was 90.3% and the specificity was 98.7%. For different cancer types, specificities and NPV remained high while sensitivities and PPV varied considerably. WTC exposure was *not* associated with accurate self-reporting.

While self-reporting of cancer diagnoses may be useful for determining non-cancer cases, the low sensitivities and PPV suggest that case confirmation from state cancer registries remains critically important.

b. Abstracts Available Only: Search Terms: "Firefighters Cancer"

Petersen KU, Pedersen JE, Bonde JP, Ebbehoej NE, Hansen J. Long-term follow-up for cancer incidence in a cohort of Danish firefighters. Occup Environ Med 2017; Oct 21; doi: 10.1136/oemed-2017-104660 (Epub ahead of print).

This is an historical study of a cohort of 9,061 Danish male firefighters using various data sets and calculating the SIRs for specific cancer types and comparing them using rates for the general population and military personnel.

The overall cancer incidence among firefighters was at a level comparable with the general population. By comparison, the SIR for colon cancer was *decreased* in firefighters. There was a slight *increase* in the SIRs for malignant melanoma, prostate, and testicular cancer in firefighters compared to the general population, but these were not different when compared with military personnel.

Abreau A, Costa C, Silva PE, Morais S, do Carmo Pereira M, Fernandes A, Moraes de Andrade V, Teixeira JP, Costa S. Wood smoke exposure of Portuguese wildland firefighters: DNA and oxidative damage evaluation. J Toxicol Environ Health 2017; 80(13-15):596-604; doi: 10.1080/15287394.2017.1286896 (Epub 2017 May 19).

Portugal is among European Union countries most devastated by forest fires, with greater than 3.8 million hectares burned in the last 3 decades.

Aim: to assess genotoxicity in a group of wildland firefighters using the comet assay for DNA damage and oxidative stress.

Both these parameters were increased in firefighters compared to controls, but reached statistical significance only for basal DNA damage.

Glass DC, Del Monaco A, Pirsher S, Hoorn V, Sim MR. Mortality and cancer incidence among male volunteer Australian firefighters. Occup Environ Med 2017; 74(9):628-638; doi: 10.1136/oemed-2016-104088 (Epub 2017 Apr 8).

Aim: to investigate mortality and cancer incidence of Australian male volunteer firefighters and subgroups defined by duration of service, era of first service, and number and types of incidents attended.

Compared with the general population, there were significant *decreases* in overall cancer incidence and most major cancer categories.

Prostate cancer incidence was *increased* compared to the general population, but was not related to the number of incidents attended.

Kidney cancer incidence was associated with increased fire attendance, in particular structural fires.

Bigert C, Gustavsson P, Straif K, Taeger D, Pesch B, Kendzia B, Schüz J, Stücker I, Guida F, Brüske I, Wichmann HE, Pesatori AC, Landi MT, Caporaso N, Tse LA, Yu IT, Siemiatycki J, Lavoué L, Richiardi L, Mirabelli D, Simonato L, Jöckel KH, Ahrens W, Pohlabein H, Tardón A, Zaridze D, Field JK, 't Mannetje A, Pearce N, McLaughlin J, Demers P, Szeszenia-Dabrowski N, Lissowska J, Rudnai P, Fabianova E, Stanescue Dumitru R, Bencko V, Foretova L, Janout V, Peters S, Vermeulen R, Kromhout H, Brüning T, Olsson AC. Lung cancer among firefighters: Smoking-adjusted risk estimates in a pooled analysis of case-control studies. J Occup Environ Med 2016; 58(11):1137-1143.

Aim: To explore lung cancer risk among firefighters.

This study used pooled information from the SYNERGY project including 14 case-control studies performed in Europe, Canada, New Zealand and China combined with lifetime work histories and smoking habits for 14,748 firefighter patients with lung cancer compared to 17,543 control subjects.

There was no increased risk of overall lung cancer or by specific cell types among firefighters, either before or after adjustment for smoking habits.

Glass DC, Pircher S, Del Monaco A, Hoorn SV, Sim MR. Mortality and cancer incidence in a cohort of male paid Australian firefighters. Occup Environ Med 2016; 73(11):761-771; doi: 10.1136/oemed-2015-103467 (Epub Jul 25).

Aim: To investigate mortality and cancer incidence among paid Australian firefighters and subgroups by era of first employment, duration of employment, and number and types of attended incidents.

The cohort was linked to the Australian National Death Index and the Australian Cancer Database. SMRs and SIRs were calculated. Separate analyses were performed for full- and part-time firefighters.

There were significant overall increases in cancer risk in firefighters compared to the general population (SIR: 1.09; 95% CI 1.03-1.14), in prostate cancer: full-time firefighters, 1.23; 95% CI 1.10-1.37 – part-time firefighters 1.51; 95% CI 1.28-1.77; and malignant melanoma, full-time 1.45; 95% CI 1.26-1.66 – part-time, 1.43; 95% CI 1.15-1.76.

Kidney cancer was associated with longer duration of service amongst paid firefighters. Prostate cancer was associated with longer service duration and increased fire attendance, particularly at structural fires.

Glass DC, Del Monaco A, Pirsher S, Vander Hoorn S, Sim MR. Mortality and cancer incidence at a fire training college. Occup Med (Lond) 2016; 66(7):536-542; doi: 10.1093/occmed/kqw079 (Epub 2016 Jul 2).

Aim: To investigate the cancer risk and mortality of those at an Australian fire training college with chronic occupational exposure risk to several chemicals. Study was conducted amongst firefighters the Country Fire Authority Fiskville (CFA) training facility between 1971-1999.

The cohort was linked to national incidence and mortality data. Standardized Mortality Ratios (SMRs) and Standardized Cancer Incidence Ratios (SIRs) were calculated.

The high-exposure group (n=95) had a clearly increased risk of cancers overall (SIR = 1.85; 95% CI 1.20-2.73), testicular cancer (SIR = 11.9; 95% CI 1.44-42.9), and malignant melanoma (SIR = 4.59; 95% CI 1.68-9.99). Brain cancer was significantly increased in the medium exposure group (n=256) (SIR = 5.74; 95% CI 1.56-14.7).

Alexander BM, Baxter CS. Flame-retardant contamination of firefighter personal protective clothing – a potential health risk for firefighters. J Occup Environ Hyg 2016; 13(9):148-155; doi: 10.1080/15459624.2016.1183016.

Aim: To characterize flame-retardant contamination on firefighter personal protective clothing to assess dermal exposure to these chemicals.

Samples from used and unused firefighter protective clothing (including gloves, hoods, and a coat waistlet) were extracted with methylene chloride and analyzed using EPA Method 8270D Specific Ion Method for polybrominated diphenyl ethers (PBDEs) which up to recently were some of the most common flame retardant materials utilized in the US.

15 of 17 PBDEs for which analyses were performed were found on at least one clothing swatch, and every clothing sample including an unused hood and all 3 layers of an unused glove had a detectable concentration of at least one PBDE.

These data suggest that firefighters have dermal exposure to PBDE flame retardants much greater than the general public, which merits further study.

Driscoll TR, Carey RN, Peters S, Glass DC, Benue G, Reid A, Fritsch L. The Australian work exposures study: Prevalence of occupational exposure to formaldehyde. Ann Occup Hyg 2016; 60(1):132-138; doi: 10.1093/annhyg/mev058 (Epub 2015 Sep 4).

Aim: To produce a population-based estimate of the prevalence of occupational-related formaldehyde exposure.

Despite many work-related potential exposures to formaldehyde, one of the common circumstances involved firefighters, fire overhaul operations, clean-up, and back-burning.

Sergentanis TN, Zagouri F, Tsilimidos G, Tsagianni A, Tseliou M, Dimopoulos MA, Psaltopoulou T. Risk factors for multiple myeloma: A systematic review of meta-analyses. Clin Lymphoma Myeloma Leuk 2015; 15(10):563-577.e1-3; doi: 10.1016/j.clml.2015.06.003 (Epub 2015 Jun 19).

Amongst 22 included meta-analyses, 9 reviewed occupational factors, 4 reviewed lifestyle aspects (smoking, alcohol use, body mass index), 5 examined presence of other co-existing diseases, and 4 reviewed potential genetic factors for potential multiple myeloma risk.

One of the significant associations found was occupation as a firefighter.

Amadeo B, Marchland JL, Moissan F, Donadieu S, Gaëlle C, Simone MP, Limbereye C, Imberon E. French firefighter mortality: analysis over a 30-year period. Am J Ind Med 2015; 58(4):437-443; doi: 10.1002/ajim.22434 (Epub Feb 23).

Aim: To evaluate the mortality of French male professional firefighters.

SMRs were calculated for 10,829 French male professional firefighters who were so employed in 1979 and compared with the French general population as of 1979-2008. The firefighters were identified from 89 French administrative departments (93% of the total firefighter population).

1,642 deaths were identified amongst the firefighter population. While the firefighter SMR increased with age, it was not statistically different from the French general population.

No significant excess of deaths was found for any specific cause in the firefighters; however, a greater number of deaths were noted from various digestive cancers (rectum/anus, pancreas, buccal-pharynx, stomach, liver, and larynx).

The authors cautioned that while non-significant excesses for digestive neoplasms were found, they should not be over-interpreted.

Pleil JD, Stiegel MA, Fent KW. Exploratory breath analyses for assessing toxic dermal exposures of firefighters during suppression of structural burns. J Breath Res 2014; 8(3):037107; doi: 10.1088/1752-7155/8/3/037107 (Epub 2014 Sep 4).

As a part of a larger NIOSH study of dermal exposure protection with safety gear used by firefighters from the city of Chicago, pre- and post-firefighting breath samples were collected and analyzed for single-ring and polycyclic aromatic

hydrocarbons, assuming that wearing of SCBA respiratory protection completely protected against inhalation exposure and that an excess exposure was due to dermal exposure.

Results: Single-ring aromatics and some PAHs were statistically significantly increased in some firefighters studies (N=15 x 2 different episodes), these levels were much lower than those found in a previous study of Air Force maintenance personnel, suggesting that firefighter's PPE may be quite effective.

Ide CW. Cancer incidence and mortality in serving whole-time Scottish firefighters 1984-2005. Occup Med (Lond); 64(6):421-427; doi: 10.1093/occmed/kqu080 (Epub 2014 Jul 7).

Aim: To determine the incidence of, and mortality from, cancer amongst a cohort of ~2,200 serving firefighters.

Service medical records were reviewed for reported cancers. The recruitment age and diagnosis was calculated and annual incidence rates and mortality rates per 100,000 population of Scottish age-matched males were compared.

Overall annual cancer incidence rates and mortality were *lower* in firefighters versus the general population. Incidence rates of malignant melanoma (13.6 versus 7.7; $p<0.001$, 95% CI 3.0-8.8) and kidney cancer (9.1 versus 4.4, $p<0.01$, 95% CI 2.4-6.7) were *higher* amongst firefighters, as was mortality from kidney cancer (6.5 versus 1.9; $p<0.01$, 95% CI 2.8-6.4).

While the incidence of testicular cancer was *higher* in firefighters, this did not reach statistical significance. Large bowel, lung, and lymphoma incidence was *lower* amongst firefighters.

Mean age and length of service were 43 years (range: 28-54) and 19 years (range: 2-31), respectively.

Pukkala E, Martinsen JI, Weiderpass E, Kjaerheim K, Lynge E, Tryggbadottir L, Sparén P, Demers PA. Cancer incidence among firefighters: 5 years of follow-up in five Nordic countries. Occup Environ Med 2014; 71(6):398-404; doi: 10.1136/oemed-2013-101803 (Epub 2014 Feb 6).

Aim: To examine the patterns among Nordic firefighters and compare them to results of previous studies.

Study data were taken from a linkage between census data for 15 million persons from 5 Nordic countries and related cancer registries for the period of 1961-2005. SIR analyses were performed with the cancer rates for the entire national populations were used as the reference rates.

16,422 male firefighters were in the final studied cohort.

A significant excess rate of prostate cancer was found in firefighters aged 30-49 years (SIR=2.59, 95% CI=1.34-4.52) and malignant melanoma (SIR=1.06, 95% CI=1.14-2.23). There were no such excesses for older age groups. In the 70 years and older age group, there were increased risks for non-melanoma skin cancers (SIR=1.40, 95% CI=1.10-1.76), multiple melanoma (SIR=1.69, 95% CI=1/08-2.51), lung adenocarcinoma (SIR=1.90, 95% CI=1.34-2.62), and mesothelioma (SIR=2.59, 95% CI=1.24-4.77).

In contrast with previous studies, testicular cancer was *decreased* (SIR=0.51, 95% CI=0.23-0.98).

These authors postulated that exposure to polycyclic aromatic hydrocarbons, asbestos, and shift work with disturbed circadian rhythms might partially account for these results.

Lacey S, Alexander BM, Baxter CS. Plasticizer contamination of firefighter personal protective clothing – a potential factor in increased health risks in firefighters. J Occup Environ Health 2014; 11(5):D43-48; doi: 10.1080/15459624.2013.877142.

Aim: To characterize semivolatile chemical contamination on firefighters' personal protective clothing (PPE) including gloves, hood, and one coat wristlet.

Swatches from these PPEs were obtained, extracted with methylene chloride, and analyzed with EPA Method 8720 for semivolative contaminants, including 20 PAHs and 6 phthalate diesters.

22/26 chemicals were found on only1 PPE swatch. Only di-(2-ethylhexyl)phthalate (DEHP) – a plasticizer added to polyvinyl chloride (PVC) to increase flexibility – was found on every tested swatch. DEHP concentrations were from 52-875 times greater than any measured PAHs. DEHP was also detected on most samples of unused firefighter PPE.

These results that firefighters are exposed to high levels of DEHP, a probable human carcinogen, at levels much higher than tested PAHs.

Paget-Bailly S, Guida F, Carton M, Menvielle G, Radoï L, Cyr D, Schmaus A, Cénée S, Papadopoulos A, Févotte J, Piloget C, Velten M, Guizard AV, Stücker L, Luce D. Occupation and head and neck cancer risk in men: results from the ICARE study, a French population-based case-control study. J Occup Environ Med 2013; 55(9):1065-1073; doi: 10.1097/JOM.0b013e318298fae4.

Aim: To investigate the associations between occupations and head and neck (HN) cancer in men.

ICARE is a French population-based case-control study on HN cancer. This study analyzed 1,833 cases and 2,747 controls. Complete occupational histories were taken and Odds Ratios (ORs) were estimated for occupations and industries ever held according to employment duration.

Elevated ORs, which increased with employment duration, were found for firefighters (OR=3.9; 95% CI=1.4-11.2).

Shaw SD, Berger ML, Harris JH, Yun SH, Wu Q, Blum A, Stefani A, Kannan K. Persistent organic pollutants including polychlorinated and polybrominated dibenzo-p-dioxins and dibenzofurans in firefighters from northern California. Chemosphere 2013; 91(10):1386-1394; doi: 10.1016/chemosphere.2012.12.070 (Epub 2013 Feb 8).

The following persistent organic pollutants were measured in the sera of 12 firefighters following a San Francisco fire event:

- Polychlorinated and polybrominated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs and PBDD/Fs)
- Polybominated biphenylethers (PBDEs)
- Polychlorinated biphenyls (PCBs)
- p,p-DDE
- Hexachlorobenzene (HCB)
- Perfluorinated chemicals (PCFs)
- Bisphenol-A (BPA)
- Tetrabromobisphenol-A (TBBPA)

TEQPCCD/F firefighters' sera concentrations were relatively low; however, 1,2,3,4,6,7,8-HpCDD – a congener indicative of firefighter exposure – were elevated.

Tentative WHO205-TEQs calculated for PBDD/Fs in firefighters' sera samples suggested that PBDD/Fs may contribute to dioxin-like toxicity in individual firefighters.

PBDE concentrations were elevated in firefighters' sera, with PBDE-209, PBDE-47, and PBDE-153 prevalent. In 4 individuals, >50% of the total PBDE concentration was PBDE-209, suggesting continuous occupational deca-BDE exposure.

Perfluorooctane sulfonate (PFOS) was the dominant PFC in firefighters' sera, followed by perfluouooctanoic acid (PFOA).

Perfluorononanoic acid (PNFA) concentrations in California firefighters were higher than those reported in the high-smoke exposure group at the NYC World Trade Center responders

These results illustrate the potential importance of monitoring halogenated contaminants including PBDD/Fs in firefighters.

Ahn YS, Jeong KS, Kim KS. Cancer morbidity of professional emergency responders in Korea. Am J Ind Med 2012; 55(9):768-778; doi: 10.1002/ajim.22068 (Epub 2012 May 24).

Aim: As firefighter and other emergency responders (ERs) in Korea are exposed to similar occupational hazards, this study was performed to assess cancer morbidity in male ERs compared to the general population of Korean men.

Cohort: 33,416 male ERs working between 1980 and 2007 who were alive on December 31, 1995. Work histories were correlated with the Korea National Central Cancer Registry (KNCCR) to assess cancer morbidity between 1996 and 2007. SIRs relative to the general population of Korean men were analyzed.

The following SIRs for specific cancers were significantly increased in all ERs:

- Colorectal: SIR=1.35; 95% CI=1.07-1.67
- Kidney: SIR=1.59; 95% CI=1.00-2.41
- Bladder: SIR=1.77; 95% CI=1.08-2.73
- Non-Hodgkin's lymphoma: SIR=1.81 ; 95% CI=1.12-2.76

Amongst firefighters, significantly increased cancer types were the same as for all ERs.

Kang D, Davis LK, Hunt P, Kriebel D. Cancer incidence among male Massachusetts firefighters, 1987-2003. Am J Ind Med 2008; 51(5):329-335; doi: 10.1002/ajim.20549.

Standardized Mortality Odds Ratios (SMORs) were utilized to assess the cancer risk of white male firefighters compared to police officers and other occupations in the Massachusetts Cancer Registry from 1986-2003.

Risks were moderately increased in firefighters for:

- Colon cancer: SMOR=1.35, 95% CI=1.04-1.79
- Brain cancer: SMOR=1.90, 95% CI=1.10-3.26

Lesser associations were found for increased risk in firefighters for:

- Bladder cancer: SMOR=1.22, 95% C= 0.89-1.69
- Kidney cancer: SMOR=1.34, 95% CI=0.90-2.01
- Hodkin's lymphoma: SMOR=1.81, 95% CI=0.72-4.53

These results are compatible with previous reports and add to the evidence that firefighters are at increased risk of a number of cancer types.

Youakim S. Risk of Cancer among firefighters: a quantitative review of selected malignancies. Arch Environ Occup Med 2006; 61(5):223-231.

This author used the fixed-effect model to quantatively estimate the risks of cancer of the colon, kidneys, brain, non-Hodgkin's lymphoma, and leukemia among firefighters.

The risk of these 6 cancers was not markedly elevated when cohort mortality studies were evaluated.

When all mortality studies were examined, however, there was a mild increased risk for:

- Kidney cancer: sumRR (summary Relative Risk)=1.22; 95% CI=1.02-1.43
- Non-Hodgkin's lymphoma: sumRR=1.40 ; 95% CI=1.20-1.60

Sub-cohort analysis based on employment duration found that firefighters with >/= 30 years had a significantly increased mortality for:

- Colon cancer: sumRR=1.51; 95% CI=1.05-2.11
- Kidney cancer: sumRR=6.25; 95% CI=1.70-16.00
- Brain cancer: sumRR=2.53; 95% CI=1.27-7.07
- Leukemia: sumRR=2.87; 95% CI=1.43-5.14

Those firefighters with >/= 40 years employment duration had a significant increased risk for:

- Colon cancer: sumRR=4.71; 95% CI=2.03-9.27
- Kidney cancer: sumRR=36.12; 95% CI=4.03-120.42
- Bladder cancer: sumRR=5.7; 95% CI=1.56-14.63

Non-Hodgkin's lymphoma risk was elevated but not significantly so in firefighters with >/= 20 years of service.

Kidney cancer risk was significantly elevated in this same group.

Guidotti TL. Evaluating causality for occupational cancers: the example of firefighters. Occup Med (Lond) 2007; 57(7):466-471; (Epub 2007 Jun 4).

Aim: To evaluate causality in selected cancer categories for firefighters using criteria applied in tort litigation and workers' compensation, based on weight-of-the-evidence as required to take into account individual factors.

Epidemiological literature evidence was reviewed on cancer risk for firefighters based on weight-of-the-evidence rather than scientific certainty.

Presumption is justified for the following cancers:

- Bladder
- Kidney
- Testicular
- Brain
- Lung (in non-smokers)

Bates MN. Registry-based case-control study of cancer in California firefighters. Am J Ind Med 2007; 50(5):339-344.

Records of all male cancers registered in California from 1988-2003 were obtained and firefighters were identified from occupation and industry text fields. Logistic regression analysis used other cancers as controls.

Of 804,000 eligible records, 3,659 had firefighting as occupation.

Firefighting was associated with:

- Testicular cancer: Odds Ratio: 1.54; 95% CI=1.18-2.02
- Malignant Melanoma: Odds Ratio: 1.50 ; 95% CI=1.33-1.70
- Brain cancer: Odds Ratio: 1.35; 95% CI=1.06-1.72
- Esophageal cancer: Odds Ratio: 1.48 ; 95% CI=1.14-1.91
- Prostate cancer: Odds Ratio: 1.22; 95% CI=1,12-1.33

LeMasters GK, Genaidy AM, Succop P, Deddens J, Sobeih T, Barriera-Viruet H, Dunning K, Lockey J. Cancer risk among firefighters: a review and meta-analysis of 32 studies. J Occup Environ Med 2006; 48(11):1189-1202.

Aim: To review 32 studies on firefighters and to make a meta-analysis, qualitatively and quantitatively, of their cancer risk.

Findings showed that firefighters have a probable cancer risk for:

- Multiple myeloma: Summary Risk Estimate (SRE)=1.53; 95% CI=1.21-1.94
- Non-Hodgkin's lymphoma: SRE=1.51 ; 95% CI=1.31-1.73
- Prostate: SRE 1.28 ; 95% CI=1.15-1.43

Testicular cancer was upgraded to *probable* because it had the highest SRE (2.01; 95% CI=1.30-3.13).

8 other cancers were listed as having a *possible* association with firefighting.

Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA. Cancer incidence in Florida professional firefighters, 1981-1999. J Occup Environ Med 2006; 48(9):883-888.

Aim: To examine the cancer risk associated with firefighting.

SIR (Standardized Incidence Ratio) analysis was used to compare the relative cancer risk of firefighters with the general Florida population.

There were 970 male cancer cases (out of 34,796 male firefighters; 413,022 person-years) and 52 female cancer cases (out of 2,017 female firefighters; 18,843 person-years).

Male firefighters had significantly increased incidences of:

- Bladder cancer: SIR=1.29; 95% CI=1.01-1.62
- Testicular cancer: SIR=1.60; 95% CI=1.20-2.09
- Thyroid cancer: SIR=1.77; 95% CI=1.08-2.73

Female firefighters had significantly increased incidences of:

- Overall cancers: SIR=1.63; 95% CI=1.22-2.14
- Cervical cancer: SIR=5.24; 95% CI=2.93-8.65
- Thyroid cancer: SIR=3.97; 95% CI=1.45-8.65
- Hodgkin's disease: SIR=6.25; 95% CI=1.26-18.26

Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA, Lai H, Lai S. Mortality in Florida professional firefighters, 1972-1999. Am J Ind Med 2004; 47(6):509-517.

Age- and gender-adjusted mortality rates of 34,796 male and 2,107 female firefighters were compared with the general Florida population.

There were 1,411 male and 38 female firefighter cancer deaths.

There was no overall excess cancer mortality, but excesses were present for:

- Male breast cancer: SMR=7.41; 95% CI=1.99-18.96
- Thyroid cancer: SMR=4.82; 95% CI=1.30-12.34

Mortality from bladder can increased and approached statistical significance (SMR=1.95; 95% CI=0.98-3.00). Firefighters certified between 1972 and 1976 had excess mortality from bladder cancer (SMR=1.95; 95% CI=1.04-3.33).

Gaertner RR, Trpeski L, Johnson KC; Canadian Cancer Registries Epidemiology Research Group. A case-control study of occupational risk factors for bladder cancer. Cancer Causes Control 2004; 15(10):1007-1019.

Aim: To investigate occupational risk factors for bladder cancer in 7 Canadian provinces.

A population-based case-control set of 887 persons with histologically-confirmed bladder cancer between 1994-1997 was compared to 2,847 controls matched for age and gender.

Modest elevated risks that were not significantly significant were observed in firefighters.

Booze TF, Reinhardt TE, Quiring SJ, Ottman RD. A screening-level assessment of the health risks of chronic smoke exposure for wildland firefighters. J Occup Environ Hyg 2004; 1(5):296-305.

This study was a screening health assessment to assess upper-bound risks for cancer and non-cancer adverse effects on health amongst wildland firefighters performing wildfire suppression and prescribed burn management.

Out of the hundreds of chemicals present in wildfire smoke, the authors identified 15 substances of potential concern, including the following:

- Aldehydes
- Polycyclic aromatic hydrocarbons (PAHs)
- Carbon monoxide
- Benzene
- Respirable particulate matter

Data reviewed included daily smoke exposures at wildfires and prescribed burns, potential days exposed to smoke/year, and career lengths.

Of the 15 studied substances, only benzene and formaldehyde were noted to have a cancer risk of >1/million.

Zeegers MP, Friesema IH, Goldbohm RA, van den Brandt PA. A prospective study of occupation and prostate cancer risk. J Occup Environ Med 2004; 46(3):271-279.

While a variety of occupations have been associated with prostate cancer in retrospective studies, these results are not able to be confidently confirmed.

A cohort study of 58,279 men (aged 55-69 years) who completed a self-administered questionnaire on potential cancer risks including an occupational history was performed in September 1986.

Moderately *decreased* prostate cancer risks were found for firefighters amongst other occupations; none of the relative risks were found to be statistically significant.

Most of the previously investigations of associations between occupation and prostate cancer risks could not be confirmed with confidence in this prospective study.

Elci OC, Akpinar-Elci M, Alavanja M, Dosemeci M. Occupation and the risk of lung cancer by histologic types and morphologic distribution: a case control study in Turkey. Monaldi Arch Chest Dis 2003; 59(3):183-188.

This was a hospital-based case-control study performed in Turkey to investigate the role occupation may play in development of lung cancer and histologic and morphologic distribution of lung cancer.

1,354 male lung cancer cases and 1,519 controls were investigated.

Excess lung cancer occurred among firefighters (OR=6.8; CI= 1.3-37.4). Firefighters had a high risk of peripheral lung cancers.

Haas NS, Gochfeld M, Robson MG, Wartenberg D. Latent health effects in firefighters. Int J Occup Environ Health 2003; 9(2):96-103.

[***Note:*** This study cannot be correlated with many others reviewed.]

This study reviewed mortality studies that used Standardized Mortality Ratios (SMRs) for firefighters. Of the 17 reviewed studies for firefighters, 3 overlapped with larger studies and 6 did not contain time-dependent data, leaving only 8 studies for inclusion.

In contrast to other studies, there was no convincing evidence that employment as a firefighter is associated with cancer mortality.

Krishnan G, Felini M, Carozza SE, Miike R, Chew T, Wrensch M. Occupation and adult gliomas in the San Francisco Bay area. J Occup Environ Med 2003; 45(6):639-647.

The etiology of gliomas is not well understood. This study compared life-time job histories of 879 patients with gliomas to those of 864 controls. The gliomas were diagnosed between August 1991 to April 1994 and May 1997 to August 1999 in the San Francisco area.

Two-fold or greater or statistically significantly elevated odds ratios (ORs) were found overall in men among those with longest-held occupations as firefighters.

Stang A, Jöckel KH, Baumgardt-Elms C, Ahrens W. Firefighting and risk of testicular cancer: results from a German population-based case-control study. Am J Ind Med 2003; 43(3):291-294.

This was a population-based case control study of 299 testicular cancer cases and 797 controls with a special focus on occupational exposures.

Three controls (0.4%) and 4 cases (1.5%) had ever worked as firefighters. Firefighters had an increased odds ratio for testicular cancer in the matched evaluation (OR=4.3; 95% CI= 0.7-30.5). Adjustment for a history of cryptorchidism and family history of testicular cancer did not alter the results.

These authors concluded that while the increased risk is based on small numbers, occupation as a firefighter may increase the risk of testicular cancer.

Austin CC, Wang D, Ecobichon DJ, Dussault G. Characterization of volatile organic compounds in smoke at municipal structural fires. J Toxicol Environ Health A 2001; 63(6):437-458.

Aim: To characterize volatile organic compounds (VOCs) found at a municipal structural fires to identify sources of long-term firefighter health risks that may be contributing factors in cancer.

Firefighters collected air inside 9 burning buildings at municipal firegrounds where they judged certain conditions might result in firefighters removing their SCBA.

VOCs were identified and quantified for 144 target compounds.

14 substances in particular were identified:

- Propene
- Benzene
- Xylenes
- 1-Butene/2-methylpropene
- Toluene
- Propane
- 1,2-Butadiene
- 2-Methylbutane
- Ethylbenzene
- Naphthalene
- Styrene
- Cyclopentene
- 1-Methylcyclopentene
- Isopropylbutylene

These 14 were in higher concentrations than found in experimental fires and accounted for 65% (SD=+/-12%) by mass of total VOCs.

Benzene or its metabolite s-phenylmercapturic acid in urine were found to be suitable markers of combustion products exposures to firefighters.

Austin CC, Wang D, Ecobichon DJ, Dussault G. Characterization of volatile organic compounds in smoke at experimental fires. J Toxicol Environ Health 2001; 63(3):191-206.

Air samples were collected from experimental fires burning commonly-found building materials seen at domicile fires and were evaluated for 144 target VOCs. The common substances found were the same as those noted in the above Abstract regarding domestic domicile fires.

Benzene was found in the highest concentrations: range=0.6-65 ppm. 1,3-Butadiene, styrene and naphthalene had peaks values of 0.1, 0.4, and 3 ppm, respectively.

No new or novel toxic non-polar VOCs were identified.

Baris D, Garrity TJ, Telles JL, Heineman EF, Olshan A, Zahm SH. Cohort mortality study of Philadelphia firefighters. Am J Ind Med 2001; 39(5):463-476.

This was a retrospective cohort study of 7,789 Philadelphia firefighters who worked between 1925-1986.

Standardized Mortality Ratios (SMRs) & 95% Confidence Intervals (CIs) were estimated. Mortality was also compared amongst firefighters by estimated number of career runs and potential for diesel exhaust exposure.

Statistically significant excess risk was found for colon cancer (SMR=1.51). There were excess risks for kidney cancer (SMR=2.20), non-Hodgkins lymphoma (SMR=1.72), and multiple myeloma (SMR=2.31) amongst firefighters with at least 20 years of service.

There was insufficient follow-up since the introduction of diesel-powered equipment to assess risk adequately.

Krstev S, Baris D, Stewart P, Dosemeci M, Swanson GM, Greenberg R, Schoenberg JB, Schwartz AG, Liff JM, Hayes RB. Occupational risk factors and prostate cancer in U.S. blacks and whites. Am J Ind Med 1998; 34(5):421-430.

This study examined occupational risk factors for prostate cancer in a larger US-based case-control study amongst black and white males.

From cancer registry data, there were 981 new pathology-confirmed cases of prostate cancer (479 blacks/502 whites) diagnosed between 1986-1989 compared with 1,315 population controls (594 blacks/721 whites) who resided in Atlanta, Detroit, or 10 New Jersey counties.

No clear occupational risk patterns were found for blacks vs. whites, or for blue-collar vs. white collar occupations.

However, risk increased with increasing years of employment as a firefighter (chi2 trend, p=0.02) and in jobs with potential PAH exposure. Overall results showed that occupation is a minor risk for prostate cancer.

Moen BE, Ovrebø S. Assessment of exposure to polycyclic aromatic hydrocarbons during firefighting by measurement of urinary 1-hydroxypyrene. J Occup Environ Med 1997; 39(6):515-519.

PAHs are present in most fires and represent a cancer risk.

Aim: To evaluate PAH exposure to students (n=9) and teachers (n=4) at a firefighter training school.

Subjects submitted urine samples before and 6-7 hours after extinguishing a burning diesel fuel fire.

Urine sample analysis for 1-hydroxypyrene levels showed that there were small, but significant, increases, indicating that firefighting may result in PAH exposure.

Feunekes FD, Jongeneelen FJ, vd Laan H, Schoonhof FH. Uptake of polycyclic aromatic hydrocarbons among trainers in a fire-fighting training facility. Am Ind Hyg J 1997; 58(1):21-28.

Personal air sampling was used to assess fire-fighting trainers for exposure to PAHs. Uptake of PAHs was assessed by measuring 1-hydroxypyrene in urine.

8-hour Time-Weighted Averages (TWA) concentrations of benzo(a)pyrene were 0.029 mcg/m^3 (instructor), 0.045 mcg/m^3 (safety officer), and 0.16 mcg/m^3 (fire assistant).

There was evidence of exposure to and uptake of PAHs among firefighting instructors despite the routine use of respirators and protective clothing.

Firth HM, Cooke KR, Herbison GP. Male cancer incidence by occupation: New Zealand, 1972-1984. Int J Epidemiol 1996; 25(1):14-21.

Aim: To identify male occupational groups with an increased incidence of cancer in New Zealand during the period of 1972-1984.

Firefighters had an increased incidence of laryngeal cancer (SIR2=1074; 95% CI=279-2776).

Deschamps S, Momas I, Festy B. Mortality amongst Paris firefighters. Eur J Epidemiol 1995; 11(6):643-646.

This was a study of a cohort of 830 male members of the Paris Fire Brigade who had served for a minimum of 5 years on January 1, 1977. They were monitored for a 14-year period ending on January 1, 1991.

A greater number of deaths than expected were found for: genito-urinary cancer (SMR=3.29), digestive cancer (SMR=1.14), and respiratory cancer (SMR=1.12).

Guidotti TL. Occupational mortality among firefighters: assessing the association. J Occup Environ Med 1995; 37(12):1348-1356.

This is a review article.

Conclusions:

- For *lung cancer*, there is evidence for an association but not of sufficient magnitude for a general presumption of risk.
- *Cancers of the genitourinary tract*: Kidney, ureter, bladder: Strong evidence for an association and for a general presumption of risk.
- *Brain cancer*: Incomplete evidence strongly suggests evidence at a magnitude consistent with a general presumption of risk.

Golden AL, Markowitz SB, Landrigan PJ. The risk of cancer in firefighters. Occup Med 1995; 10(4):803-820.

Carcinogenic substances to which firefighters may be exposed:

- Benzene
- Asbestos
- PAHs
- Formaldehyde
- Diesel exhaust

Firefighter cancers of concern (prevalent):

- Leukemia
- Non-Hodgkin's lymphoma
- Multiple myeloma
- Brain cancer
- Bladder cancer

Figgs LW, Dosemeci M, Blair A. United States non-Hodkin's lymphoma surveillance by occupation 1984-1989: a twenty-four state death certificate study. Am J Ind Med 1995; 27(6):817-835.

Death Certificates from 23,890 male and female non-Hodgkins lymphoma cases and 119,450 non-cancer controls from 24 US States for the period of 1984-1989 were used to generate hypotheses about occupational associations.

Significant observations were noted for *firefighters*.

Delahunt B, Bethwaite PB, Nacey JN. Occupational risk for renal cell carcinoma. A case-control study based on the New Zealand cancer registry. Br J Urol 1995; 75(5):578-582.

This was a study using the New Zealand Cancer Registry from 1978-1986.

A significantly increased risk was found for firefighters for development of renal cell carcinoma (RR=4.89; 95% CI=2.47-8.93).

Muscat JE, Wynder EL. Diesel exhaust, diesel fumes, and laryngeal cancer. Otolaryngol Head Neck Surg 1995; 112(3):437-440.

This was a hospital-based case-control study of 235 male patients with laryngeal cancer and 205 controls to assess the potential of exposure to diesel exhaust and diesel fumes as a risk factor.

Occupations that could involve such exposures included firefighters

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After analysis, these authors concluded that exposure to diesel exhaust and fumes was *not* related to an increased risk of laryngeal cancer.

Demers PA, Checkoway H, Vaughan TL, Weiss NS, Heyer NJ, Rosenstock L. Cancer incidence among firefighters in Seattle and Tacoma, Washington (United States). Cancer Causes Control 1994; 5(2):129-135.

Aim: To examine the risk of cancer in a cohort of 2,447 male firefighters in Seattle and Tacoma.

The study population was followed for 16 years (1974-1989) and the incidence of cancer was determined by using a population-based tumor registry and was compared with local rates among police officers from the same region.

The risk of cancer was found to be similar to that of police officers and the general male population.

An increased risk of *prostate cancer* was found relative to the general population and was not related to the duration of exposure.

The relationship of firefighting exposure and colon cancer was consistent with other studies, it is based on small numbers, and could be due to random chance.

Guidotti TL. Mortality of urban firefighters in Alberta, 1927-1987. Am J Ind Med 1993; 23(6):921-940.

Certain causes of death are likely to be associated with firefighting (e.g., lung cancer).

As well, certain other cancers including those of the genitourinary tract, colon and rectum, certain leukemias, lymphomas, and multiple myeloma also seem to be elevated among firefighters.

One as yet to be proven hypothesis is that such increased cancer risks followed the introduction of building materials made up of combustible plastics that can release toxic combustion products when burning or smoldering.

In two cohorts (before and after the 1950s when combustible plastic furnishings and building products came into use) with a total of 3,328 firefighters working from 1927-1987 in the Canadian cities of Edmonton (Alberta, Canada) and Calgary (Alberta, Canada), this study examined the cohorts for years of firefighting service weighted by opportunity for exposure.

A 96% follow-up of vital statistics was achieved and more than 64,983 person-years observation found 370 deaths.

Excesses were found for all malignant neoplasms (SMR=127; 95% CI=102-155; $p<0.05$), and for:

- Lung cancer: SMR=142; 95% CI=91-211; not significant
- Bladder cancer: SMR=315; 95% CI=86-808; $p<0.05$
- Kidney and Ureter cancer: SMR=155; 95% CI=50-362; not significant
- Leukemia, Lymphoma, and Myeloma: SMR=15; 95% CI=79-281; not significant

There was no consistent association with employment duration, opportunity for exposure, or entry cohort (before of after the 1950s). The highest risk was in firefighters with more than 35 weighted years of service.

Demers PA, Vaughan TL, Keppel TD, Lyon JL, Swanson GM, Greenberg RS, Weiss NS. A case-control study of multiple myeloma and occupation. Am J Ind Med 1993; 23(4):629-639.

Life-time job histories from a population-based case-control study were used to evaluate the potential relationship between employment in various occupations and development of multiple myeloma. Interviews were able to be conducted with 692 (89%) of eligible cases and from 1,683 (83%) of case-control subjects.

Various occupations had an elevated multiple myeloma risk (odds ratios), and there was some evidence based on small numbers of an association with firefighting.

Ford J, Smith S, Lou JC, Friedman-Jimenez G, Brandt-Ralf P, Markowitz S, Garibaldi K, Nyman H. Serum growth factors and oncoproteins in firefighters. Occup Med (Lond) 1992; 42(1):39-42.

Growth factors and oncogene proteins are thought to have a role in the development of cancers. Firefighters are potentially at increased risk of developing cancer.

Aim: To screen a cohort of firefighters and matched controls for the presence of 9 different growth factors and oncoproteins with an immunoblotting assay.

Fourteen of the screened firefighters had positive results for beta-transforming growth factor (β-TGF) related proteins as compared to no positive results in the controls ($p=0.0017$).

These data suggest that β-TGF maybe useful as a biomarker for monitoring firefighters for the potential development of cancer.

Beaumont JJ, Chu GS, Jones JR, Schenker MB, Singleton JA, Piantanida LG, Reiterman M. An epidemiologic study of cancer and other causes of mortality in San Francisco firefighters. Am J Ind Med 1991; 19(3):357-372.

Aim: To test the hypothesis that firefighter exposures may increase cancer risk.

Mortality rates were determined for 3,066 San Francisco firefighters employed from 1940 to 1970 (vital statistics determined through 1982) and compared to the US general population death rates.

The total number of deceased firefighters was less than expected and total cancer deaths were less than expected. There was a significant excess number of deaths from esophageal cancer (12 observed, 6 expected).

Sama SR, Martin TR, Davis LK, Kriebel D. Cancer incidence among Massachusetts firefighters, 1982-1986. Am J Ind Med 1990; 18(1):47-54.

Aim: To perform case-control studies to determine associations between cancer incidence and firefighting amongst a cohort of Massachusetts firefighters.

Nine different types of cancer were evaluated among 315 reported white male fighters. Reference populations were: police officers and Massachusetts statewide males.

Standardized Morbidity Odds Ratios (SMORs) were statistically significantly increased in firefighters compared to statewide males for:

- Malignant melanoma (SMOR=92; 95% CI=170-503)
- Bladder cancer (SMOR=159; 95% CI=102-104)

When police officers were used as the reference group, the following were found:

- The bladder cancer increase persisted (SMOR=211; 95% CI=107-414)
- Non-Hodgkin's lymphoma was increased (SMOR=327; 95% CI=119-898)
- Excess malignant melanoma was *reduced* (SMOR=138; 95% CI=60-319), but remained *increased* amongst firefighters aged 55-74 years (SMOR=513; 95% CI=150-1,750)
- Small numbers, but not statistically significant, excesses were found amongst firefighters for:
    - Pancreatic cancer
    - Leukemia

Zahm SH, Brownson RC, Chang JC, Davis JR. Study of lung cancer histologic types, occupation, and smoking in Missouri. AmJ Ind Med 1989; 15(5):565-578.

Aim: To perform a case-control study of certain histological types of lung cancer and occupation, adjusted for tobacco smoking.

A total of 4,431 lung cancer cases and 11,326 controls were evaluated using data from the Missouri Cancer Registry.

The incidence of lung cancer was significantly elevated for patients employed in various occupations. For firefighters, the Odds Ratio (OR) was 1.6; 95% CI=1.1-2.3.

Feuer E, Rosenman K. Mortality in police and firefighters in New Jersey. Am J Ind Med 1986; 9(6):521-527.

Aim: To perform a proportionate mortality study of New Jersey firefighters using records from a comprehensive retirement system, as compared to 3 reference populations:

- The general US population
- The New Jersey general population
- New Jersey police officers

Analyses by latency revealed an excess increase in skin cancer amongst firefighters.

Firefighters had a significant increase in leukemia (PMR=2.76) when police officers were used as the reference group.

c. Abstracts Available Only: Search Terms: "Fire Smoke Carcinogens"

Laitinen J, Mäkelä K, Mikkola J, Huttu I. Fire fighting trainers' exposure to carcinogenic agents in smoke diving simulators. Toxicol Lett 2010; 192(1):61-65; doi: 10.1016/toxlet.2009.06.864 (Epub 2009 Jul 1).

A largely unheeded source of firefighter exposure to potential carcinogens is in smoke diving simulators.

Biomonitoring was carried out in this study:

- Urinary: muconic acid, 1-napthol, 1-pyrenol
- Dermal: polycyclic aromatic hydrocarbons, formaldehyde
- Industrial Hygiene: polycyclic aromatic hydrocarbons, volatile organic compounds, formaldehyde

The safest burning material was propane.

Highest PAHs exposure was in the fire house simulator; 35% lower exposures were found in container training sessions, and exposure levels in the propane simulator were only 4% of those in the container simulator.

PAHs on trainers hands decreased by 80% when under-gloves were worn. Of two different firefighters' suits tested, there was no difference in the protection efficiency against PAHs.

Fernando S, Shaw L, Shaw D, Gallea M, VandenEnden L, House R, Verma DK, Britz-McKibbin P, McCarry BE. Evaluation of firefighter exposure to wood smoke during training exercises at burn houses. Environ Sci Technol 2016; 50(3):1536-1543; doi: 10.1021/acs.est.5b0472 (Epub 2016 Jan 20).

Wood smoke has a complex nature and contains many components which include methoxyphenols (MPs) and polycyclic aromatic hydrocarbons (PAHs), some of which are carcinogenic.

From a cohort of 28 firefighters at training exercises in burn houses in Ontario, Canada, air samples, skin wipe samples, and urine samples were obtained before and after primarily wood smoke exposure.

The air sampling showed that levels of MPs were 5 times > than those of PAHs. The skin wipe samples found whole-body exposure to the wood smoke. In the urine, a group of MPs (methyl-, ethyl-, and propylsyringol) and deconjugated PAH metabolites (hydroxynaphthylene, hydroxyfluorene, hydroxyphenanthrene and their isomers) were noted to be sensitive markers of wood smoke exposure. Creatinine-normalized levels of the urinary markers were significantly increased at 24-hours post-wood smoke exposure. There was considerable subject-to-subject variation which depended on the subjects operational roles during the exercises.

Recommendations: Improved protective equipment to mitigate skin exposures and dermal absorption; standardized hygiene practices.

Golka K, Weistenhöfer W. Fire fighters, combustion products, and urothelial cancer. J Toxicol Environ Health B Crit Rev 2008; 11(1):32-44; doi: 10.1080/10937400701600396.

A review of the literature on combustion products and the risk of urogenital cancer in firefighters.

Chemical analysis of smoke from experimental fires and fires in cities, woodlands, and industry do not find a generally increased risk of urogenital cancer in firefighters.

Based on mortality studies, exposure studies, and cancer incidence led to the conclusion that an increased risk of urogenital cancer in firefighters could not be confirmed. However, in professional firefighters with decades of service, occupational chemical exposures might be considered as causative for urogenital cancer.

Melius J. Occupational health for firefighters. Occup Med 2001; 16(1):101-108.

Firefighters are routinely exposed to a large number of toxic chemicals. Those which may be carcinogenic include:

- Benzene
- Particulates
- Asbestos
- Polynuclear aromatic hydrocarbons (PAHs)

Driscoll TR, Carey RN, Peters S, Glass DC, Benke G, Reid A, Fritschi L. The Australian work exposure study: Occupational exposure to polycyclic aromatic hydrocarbons. Ann Occup Hyg 2016; 60(1):124-131; doi: 10.1093/annhyg/mev057 (Epub 2015 Aug 31).

Aims: To produce a population-based estimate of the prevalence of work-related exposures to PAHs and describe workplace control methods to decrease such exposures.

Of 4,933 respondents, 297 (5.9%) were probably exposed to PAHs in their current jobs. Most (81%) were male. Main PAHs exposures were to smoke, including those of firefighters.

2. **Other Papers, Presentations, and Documents of Interest**

Shimizu Y, Nakatsuru Y, Ichinose M, Takahashi Y, Kume H, Mimura J, Fujii-Kuriyama Y, Ishikawa T. Benzo[a]pyrene carcinogenicity is lost in mice lacking the aryl hydrocarbon receptor. PNAS 2000; 97(2):779-782.

While the aryl hydrocarbon receptor (AhR) has been extensively studied for its role in induction of xenobiotic modulating enzymes, no direct evidence that AhR plays a role in carcinogenesis currently exists.

Aim: To determine whether AhR plays a role in cancer induction, the response of AhR-deficient mice to the well-known environmental carcinogen, benzo[a]pyrene was studied.

Benzo[a]pyrene induced expression of the Cyp1a1 gene in the skin and liver of AhR positive mice (AhR +/+ and AhR +/-), but did not induce such expression in AhR negative (AhR -/-) mice in either liver or skin.

In contrast, expression of the Cyp1a2 gene was positive in the liver in both AhR positive and negative mice.

All the AhR positive mice (AhR +/+ and +/-) injected subcutaneously on days 1 and 8 developed subcutaneous tumors at the injection site during the 18-day study. All tumors were solitary. On histology examination, most tumors were fibrosarcomas; there were also 3 squamous cell carcinomas and 3 rhabdomyosarcomas. No notable difference in tumors between AhR +/+ and +/- mice was found. All tumors formed tumors when implanted into the back skin of nude mice, confirming their neoplastic nature. In female mice, the histologic tumor types were mostly squamous cell carcinomas with some papillomas and keratoacanthomas noted. No tumors occurred in the AhR negative (AhR -/-) mice. The was a statistically significant difference between AhR +/- and AhR -/- mice ($p<0.01$).

When benzo[a]pyrene was applied topically at weekly intervals to female mice, skin tumors were only found in the AhR positive (AhR +/+ or +/-) mice.

As a comparison, when 4-nitroquinolone-1-oxide which is metabolically activated by a quite different pathway was applied to the skin of AhR+/+, AhR +/-, and AhR -/- mice, tumors (papillomas and squamous cell carcinomas) occurred equally in all 3 AhR types.

These authors concluded that the carcinogenic action of benzo[a]pyrene may be primarily determined by AhR, a transcriptional regulator of the CYP1a1 gene.

Tilton S. Evaluating carcinogenic risk for mixtures with systems biology data. Presented at the Society of Toxicology Annual Meeting, San Antonio, Texas, March 9-15, 2018.

Hypothesis: short-term bioactivity profiles can be prognostic for cancer outcomes from exposure to individual PAHs and complex PAH mixtures.

Aim:

- To identify bioactivity profiles following short-term exposures for PAHs and PAH mixtures to develop a "chemical fingerprint"
- To classify PAH exposures utilizing a pathway-driven approach based on potential carcinogenicity
- To identify key biological pathways predictive of cancer outcomes and evaluate mechanisms which likely contribute to carcinogenic MOA (Modes of Action)
- To develop data contributing to a whole-mixture approach for risk assessment

Current Paradigm:

- PAH exposure
- PAH metabolism
- Initiation: DNA adduct formation; mutation
- Promotion: Ah receptor binding; gene up-regulation; initiated cells proliferation; cytotoxicity; inflammatory response
- Progression: Neoplasm development

New Paradigm:

- Evaluation of the global response following exposure
- Modeling which processes are associated with PAH and PAH mixtures carcinogenesis

3 Ways to evaluate the toxicity of PAH mixtures:

- *Component-based approach*: quantify diverse PAHs and identify biologically relevant fractions
- *Whole mixture approach*: evaluate complex environmental mixtures for biological or mechanistic response(s)
- *Surrogate approach*: evaluate toxicity to simplified synthetic/composite mixtures

One approach to PAH mixtures is to use RPF (Relative Potency Factors) for various PAHs in a mixture, which leads to uncertainty because:

- This assumes development of cancer is the most sensitive endpoint
- Assumes that certain priority PAHs are representative of the mixture (may either over- or under-estimate the toxicity of the whole mixture); there are also limited data on many components of PAH mixtures
- Assumes additivity of PAH mixture components (ignores evidence for inhibitory reactions for various components) and many interactions are simply unknown
- When making estimates of carcinogenic potency relative to benzo[a]pyrene, assumes that there are common RPFs, and other traditional endpoints; PAHs may have multiple mechanisms of action for carcinogenesis with evidence for both genotoxic and non-genotoxic actions

2 Case Studies were described in this presentation:

- A 2-stage skin tumor model in 6-week old FVB/N mice, where the following points were noted:
    - Pathways of carcinogenic potential of PAHs and mixtures were used appropriately to classify chemicals based on outcome
    - PAHs function in carcinogenicity by different mechanisms of action
    - In mixtures, PAHs are not strictly additive
    - There is a potential for whole-mixture assessments based on molecular endpoints
        - It may be possible to assess whole-mixtures without complete knowledge of the components or potential interactions

- An airway organotypic culture model for toxicity assessment, whose benefits might be:
    - A 3-D structure
    - Metabolic and mitotic activity
    - Multicellular communication and cell signaling
    - Model more accurately reflects exposure at tissue interfaces
    - Better reflects *in vivo* responses

Firefighter Cancer Support Network. Taking action against cancer in the Fire Service. White paper. August (V2), 2013.

Multiple studies have shown that firefighters have the following increased risks of a number of cancers:

Cancer Type	Increased Risk (As Compared to the USA General Population)
Testicular Cancer	2.02 Times Greater Risk
Multiple Myeloma	1.53 Times Greater Risk
Non-Hodgkin's Lymphoma	1.51 Times Greater Risk
Skin Cancer	1.39 Times Greater Risk
Prostate Cancer*	1.28 Times Greater Risk
Malignant Melanoma	1.31 Times Greater Risk
Brain Cancer	1.31 Times Greater Risk
Colon Cancer	1.21 Times Greater Risk
Leukemia	1.14 Times Greater Risk
Breast Cancer (in Females)	Preliminary Study Results from the San Francisco, CA Fire Department

*Note: The increased risk of prostate cancer is somewhat difficult to understand. During a period of evaluating whether any specific chemical exposures in populations of contract workers at nuclear weapons production facilities and test sites, a number of medical specialists (including myself) evaluated the literature quite extensively. The only potential chemical

exposure that was found was *zinc*, and this was based on the rather unique metabolic handling of zinc by the prostate. No actual evidence that zinc exposure was causal for prostate cancer was found and no other chemical exposure(s) resulting in prostate cancer were noted at that time. However, the IARC Monograph on Cadmium and Compounds does mention that some associations have been seen between cadmium exposure and kidney and prostate cancer.

The major risk factors that were clear from our evaluation were: male gender; age >40-50 years. The risk increased with advancing male age, such that in some autopsy studies, the incidence of at least prostate cancer *in situ* was found in 80-90% of all males studied. The use of Prostate Specific Antigen (PSA) testing as a predictive biological marker was formerly widely used, but has fallen into some skepticism as it seems to be too sensitive and leads to (in retrospect) unnecessary non-invasive and invasive diagnostic procedures and perhaps unnecessary surgical interventions. It is therefore possible, although not proven, that professional firefighters who have a comprehensive health screening program available, might therefore have the possibility of having prostate cancer suspected or diagnosed while members of the US general population (many who do not have such programs) might have the same incidence of which at least some remain undetected.

DISCUSSION

International Agency for Research on Cancer (IARC) Classifications (IARC, 2018):

IARC Group	Classification Explanation
Group 1	Carcinogenic to Humans
Group 2A	Probably Carcinogenic to Humans
Group 2B	Possibly Carcinogenic to Humans
Group 3	Not Classifiable as to its Carcinogenicity to Humans
Group 4	Probably not Carcinogenic to Humans

From all of the above review, a list of chemical to which firefighters may be exposed occupationally together with their IARC Classifications follows (Hathaway and Proctor, 2004; HSDB, 2018; IARC, 2018):

References

1. Hathaway GJ, Proctor NH (eds). Proctor & Hughes' Chemical Hazards of the Workplace, 5th ed. John Wiley & Sons, Hoboken, NJ, 2004.
2. HSDB (Hazardous Substances Data Bank). US National Library of Medicine, Bethesda, MD, http://www.nlm.nih.gov/hsbd (Accessed April 12-20, 2018).
3. IARC (International Agency for Research on Cancer). Lyon, France, http://www.monographs.iarc.fr (Accessed May 5-15, 2018).

Asbestos

IARC Classification: Group 1

- Sufficient evidence in humans and experimental animals
- This agent is carcinogenic to humans

Inhalation is the major exposure route to this group of hydrated mineral silicates found as fibers.

Asbestos cancer endpoints:

- Bronchogenic carcinoma
- Pleural/peritoneal mesothelioma
- Mesothelioma may occur after a short, very intensive asbestos exposure.
- A latent period between moderate-level exposure and development of mesothelioma of 20-30 years is not uncommon.

Recommendation: Neither of the two current test models Prevor has been researching (mouse skin exposure model or Epithelix Mucilair® respiratory epithelia model seem amenable to testing with asbestos as it is not absorbed through the skin and the Mucilair® model is too short-term and lacks pleura.

Metals/Metalloids

Metal/Metalloid	IARC Classification
Antimony	
Trioxide	2B
Trisulfide	3
Arsenic	
Arsenic and Inorganic Compounds	1
Dimethyl- and Mono-methyl Arsonic Acids	2B
Arsenobetaine and Other Similar Organoarsenical Compounds	3
Cadmium and Compounds	1
Lead	
Inorganic Compounds	2A
Organic Compounds	3
Mercury	
Methylmercury Compounds	2B
Metallic and Inorganic Compounds	3
Uranium	
Metal and Non-Radioactive Compounds	Not Classified*

*The American Conference of Governmental Hygienists (ACGIH) considers Uranium Metal and Soluble and Insoluble Compounds as Confirmed Human Carcinogens (HSDB, 2018).

> **Recommendation:** The above metals/metalloids and their compounds would not be appropriate for study in the mouse skin exposure model. Arsenic is known to cause various skin cancers, but the most common exposure route is long-term ingestion of contaminated groundwater.

Volatile Organic Compounds

Aromatic

Aromatic Compound	IARC Classification
Benzene	1
Ethylbenzene	2B
Styrene	2B
Toluene	3
m-/p-Xylenes	3

Recommendation: Of these, *benzene* might be considered for study in the mouse model as it is a known human carcinogen and is well-absorbed through the skin. However, its primary carcinogenic effects are on the hematopoietic system and require metabolism to various metabolites. This would seem to be very limiting in the current mouse skin assay.

Other VOC s

VOC	IARC Classification
1,2-Butadiene	None
1-Butene/2-Methylpropene	None
Cyclopentene	None
N-Hexane	None
Isopropylbutylene	None
1-Methylcyclopentene	None
Naphthalene	2B
Propane	None
Propene	None

Recommendation: The only compound in this group of potential interest is naphthalene (2B). However, as there are other compounds classified by IARC in Group 1, naphthalene would not seem to be a priority for study in the mouse skin exposure model.

Polycyclic Aromatic Hydrocarbons (PAHs) and Metabolites

PAHs and Metabolites	IARC Classification
Benzo[a]pyrene	1
Benzofluoranthracene	3
1-Hydroxypyrene	None
1-Hydroxyphenanthrene	None
2-Hydroxyphenanthrene	None
3-Hydroxyphenanthrene	None
Benzo[a]pyrenediol epoxide	None
Hydroxyfluorene	None

Recommendation: The only IARC Classification 1 in this group is benzo[a]pyrene. It could be considered for further study in the mouse model.

Miscellaneous Compounds Mentioned in the Literature Searches

Compound	IARC Classification
Bisphenol-A	3
1,4-Dichlorobenzene	3
p,p-DDE	None (DDT is 2B)
di-(2-Ethylhexyl)phthalate [DEHP]	2B
Hexachlorobenzene [HCB]	2B
Methyl-tert-butyl ether	3
Perfluorooctane sulfonate [PFOS]	None
Perfluorooctanoic acid	2B
Tetrabromobisphenol-A [TBBPA]	2A
Vinyl chloride	1

Recommendation: The only IARC Classification 1 in this group is vinyl chloride. However, vinyl chloride has really only been known to cause hepatic cancer in workers in the polyvinylchloride (PVC) industry who used to clean out the industrial-sized mixers without protective equipment. It would not seem suitable for study in the mouse model.

Classes of Compounds

Compound Class/ Specific Compound(s)	**IARC Classification**
Aldehydes	
Acetaldehyde	Evidence in Humans is Inadequate
Acrolein	Evidence in Humans is Inadequate
Dioxins	
2,3,7,8-Tetrachlorodibenzo-p*ara*-dioxin	1
Other polychlorinated dibenzo-p*ara*-dioxins and dibenzo-*para*-dioxin	3
Methoxyphenols (MPs)	None
Perfluorinated chemicals	None
Phthalate diesters	
De-(2-Ethylhexyl)phthalate	2B
Polybrominated dibenzofurans	2A
Polybrominated diphenyls (PBBs)	2A
Polychlorinated biphenyls (PCBs)	2A

Recommendation: Given the great variation in these groups of compounds and the many, many individual specific chemicals contained therein, it will require much consideration to determine if any are appropriate for Prevor studies.

Diesel Exhaust

Diesel exhaust has an IARC Classification of 1.

Occupation as a Firefighter

Occupational as a firefighter has an IARC Classification of 2B.