Chemical Substances and Biological Agents

Studies and Research Projects

REPORT **R-518**

Risk of Leukaemia in Firemen

Douglas McGregor

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Leukaemia

Leukaemia is a collection of progressive, malignant diseases of the blood-forming organs, characterised by distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Haematological malignancies are primarily grouped according to lineage: myeloid, lymphoid, histiocytic/dendritic cell and mast cell, and according to the degree of cell differentiation as acute or chronic. In epidemiological reports, including those relating to occupational risks encountered by firemen, there is frequently no distinction drawn between these groups. Nevertheless, is as well to be aware that haematopoietic and lymphoid neoplasms are a heterogeneous collection of distinct diseases that in recent years have been classified by the World Health Organisation according to a combination of morphology, immunophenotype, genetic features and clinical syndromes (WHO, 2001). The relative importance of each of these features varies among the diseases and there is no "gold standard." For some of the myeloid neoplasms, the cell of origin is known to be a pluripotential or multipotential stem cell, but for lymphoid neoplasms the cell of origin is often not known and so it is simply stated to be the stage of differentiation that is actually observed. There are four major groups of myeloid diseases:

(1) Chronic myeloproliferative diseases that are clonal stem cell disorders characterised by effective haematopoiesis, resulting in elevated peripheral blood levels of one or more cell lines and, usually, hepatosplenomegaly; there is bone marrow hypercellularity with maturation and without dysplasia;
(2) Myelodysplastic syndromes that are clonal stem cell disorders characterised by ineffective haematopoiesis, resulting in cytopaenias and dysplastic maturation of one or more cell lines;
(3) Myelodysplastic/myeloproliferative diseases are clonal stem cell disorders that have features overlapping those of (1) and (2), with variably effective haematopoiesis and dysplastic features;
(4) Acute myeloid leukaemias that are clonal expansions of myeloid blasts and themselves form a heterogeneous grouping, with different cytogenetic, myelodysplasia related and therapy related features

There are three major categories of lymphoid neoplasms:

(1) B cell neoplasms,
(2) T and NK cell neoplasms and
(3) Hodgkin lymphoma.

Both lymphoid leukaemia and lymphomas are included in this classification, the distinction between circulating and solid forms or phases of these neoplasms being considered artificial. The peripheral T/NK cell and B-cell neoplasms are grouped according to their most typical clinical presentations: predominantly disseminated, leukaemic, primary extranodal lymphomas and predominantly nodal lymphomas.

Multiple myeloma, or plasma cell myeloma (ICD-O code 9732/3), is a multifocal neoplasm based in bone marrow and derived from the clonal expansion of immunoglobulin-secreting, terminally differentiated B cells. However, multiple myeloma usually has been reported separately from leukaemia, so the evidence for occupational exposures of firemen being a risk factor for this disease will be treated separately (*Risk of Multiple Myeloma and Cancers of the Respiratory System, Oesophagus, Stomach, Pancreas, Prostate, Testes and Skin in Firemen*)

Similarly, “non-Hodgkin lymphoma” (NHL) has been assessed in the context of occupational exposures among firemen in a separate document. It is, in fact, any of a group of malignant tumours of lymphoid tissue that differ from Hodgkin disease by being more heterogeneous with respect to malignant cell lineage, clinical course, prognosis, and therapy. The only common feature among these tumours is the absence of giant Reed-Sternberg cells, which are a characteristic of Hodgkin's disease. Therefore, there is most likely an overlap of the leukaemias considered here and the NHL considered in the other document.

Epidemiology of Leukaemia

Leukaemia comprises about 3% of the worldwide cancer incidence, there being about 260,000 new cases annually. Incidence rates vary from about 1 to 12 per 100,000, the lower rates occurring in most African and Asian countries. Trends in overall incidence have been either stable or slowly increasing. There is a peak in leukaemia incidence in the first four years of life that is mainly due to acute lymphoblastic leukaemia; this accounts for about 25 % of childhood malignancies. The lowest incidence occurs at age 15 to 25 years, after which there is an exponential increase with age, up to about 85 years when the risk is about 300-fold greater than it is during the second decade of life. Age-standardised incidence rates in males for leukaemia as a group, multiple myeloma and immunoproliferative diseases in Canada and Québec are shown in Figure 1. There is little difference between Québec alone and Canada as a whole for any of these disease groups.

In adults, acute myeloid leukaemia accounts for 80-85% of all cases of acute leukaemia diagnosed in people of >20 years of age (Schiffer & Stone 2000). Chronic forms of leukaemia are mainly adult diseases that rarely develop below 30 years and then increase with age; chronic myelogenous leukaemia accounting for 15 – 20% of all leukaemias, while for patients > 50 years chronic lymphocytic leukaemia is dominant.

The study of effects of any exposure on leukaemia presents a problem because leukaemia is not one disease with a specific aetiology, but a combination of several diseases that may have different causes. It would be desirable to consider separately at least four diseases in adults: acute myeloid, chronic myeloid, acute lymphoid and chronic lymphoid leukaemia. Unfortunately, most studies do not make any distinction between even these few forms of the disease and group them simply as leukaemia, or even lymphoid and haematopoietic neoplasms combined. Risk factors for most forms of leukaemia have not been identified. Occupational exposure to benzene has been associated with acute myeloid leukaemia (IARC, 1987) and more recently tobacco smoking has been identified as a cause of the disease (IARC, 2004). Risk increased with amount of tobacco smoked in a substantial number of studies considered adequate for evaluation and support for a causal relationship comes from the finding that benzene is present in sufficient quantities to account for up to half of the estimated excess cases of acute myeloid leukaemia. In contrast, no clear evidence of any risk has been found for lymphoid leukaemia/lymphoma as a consequence of exposure to tobacco smoke.

Two case-control studies of leukaemia from the USA reported an elevated relative risk for myeloid leukaemia amongst welders, but no overall excess risk for either

acute or all leukaemia was observed in a pooled analysis of data from several studies of welders (IARC, 1990).

Mainly acute myeloid leukaemia increases are also associated with exposure to ionizing radiation and medical procedures using cyclophosphamide, melphalan, thiotepa, treosulphan, etoposide, teniposide or mitoxantrone and following the induction of aplastic anaemia by the antibiotic chloramphenicol. Infection with the virus HTLV-1 is a cause of adult T-cell leukaemia, which is rare in northern America and Europe and is mainly observed in Japan and tropical countries (WHO, 2003).

A prospective study of a cohort for effects of body weight on mortality from cancer in more than 900,000 U.S. adults followed from 1982 included 57,145 deaths from cancer during a 16-year follow-up period (Calle et al., 2003). Body mass indices were measured at entry and the population divided according to body mass index (BMI). Risk ratios for leukaemia was increased with increasing BMI as follows:

Neoplasm	**BMI 18.5-24.9**	**BMI 25.0-29.9**	**BMI 30.0-34.9**	**BMI 35,0-39.9**
Leukaemia				
No. of deaths	546	720	128	20
Death rate*	22.51	25.60	30.40	40.52
RR (95%CI)	1.00	1.14 (1.02-1.28)	1.37 (1.13-1.67)	1.70 (1.08-2.66)

This study suggests that excess body weight is a potential confounder for leukaemia.

Firemen: General Characteristics and Exposures

The task of fire fighting consists of two phases: (1) *knockdown*, during which the fire is brought under control, and (2) *overhaul*, when the fire is extinguished and clean up begins. Approximately 90% of structural fires are either extinguished or abandoned and fought from outside within 5 – 10 min., the average duration of heavy physical activity being 10 min. (Gilman & Davis, 1993). Although self-contained breathing apparatuses (SCBA)s are available, these are seldom worn from the time the firemen arrive at the scene until the time that they leave. In a study of exposures in the City of Montréal fire department, Austin et al., 2001a, found that SCBAs were worn about 50% of the time at structural fires, but they were worn for only 6% of the total time spent at all types of fires. Masks are generally put on when the firemen enter a fire or "see smoke," but it is difficult for them to judge when the mask can be safely removed and they are rarely worn during the smouldering phase of a fire or during mop-up operations. Furthermore, communication is essential and this is difficult with the mask in place. The largest category of non-fatal fire fighter injuries associated with fires has been reported to be contact with flames and smoke (39%) and the leading cause of non-fatal injury among younger firemen is related to smoke inhalation (FEMA, 1990).

In a study of municipal structural fires, Austin et al., 2001b found that just 14 different compounds accounted for about 75% of the total volatile organic materials measured (Table 1). These same compounds constituted approximately 65% of all volatile organic compounds in experimental fires burning various materials commonly found in structural fires (Austin et al., 2001c). The spectra of volatile organic compounds were dominated by benzene along with toluene and naphthalene. They also found that propylene and 1,3-butadiene were present in all of the fires and

that styrene and other alkylated benzenes were frequently identified. Other materials that have quantified with some regularity include acrolein, carbon monoxide, formaldehyde, glutaraldehyde, hydrogen chloride, hydrogen cyanide and nitrogen dioxide (Bolstad-Johnson et al., 2000; Caux et al., 2003). There may also be exposure to asbestos and various metals, such as cadmium, chromium and lead. In addition, there is almost certainly exposure to diesel exhaust and fumes and to polycyclic aromatic hydrocarbons (PAHs).

During overhaul, recommended ceiling or short-term exposure levels can often be exceeded, e.g., for acrolein, benzene, carbon monoxide, formaldehyde, glutaraldehyde, nitrogen dioxide and sulphur dioxide (Bolstad-Johnson et al., 2000) and several of these, e.g., carbon monoxide and benzene, were found to be present at appreciable concentrations in the atmosphere at real fire scenes when SCBAs were only used part of the time or not at all, owing to the impression that there was low smoke intensity (Brandt-Rauf et al., 1988, 1989).

Possible risk factors for leukaemia associated with fighting fires.

Certain exposures to possibly carcinogenic materials, such as polycyclic aromatic hydrocarbons (PAH), benzene, 1,3-butadiene and diesel exhaust, are associated with fighting fires. The evidence for their involvement in the diseases being reviewed here will be briefly summarised, as will consideration of the effect of tobacco smoke, because it has components in common with those encountered by firemen in their work.

1,3-Butadiene. A cohort study of workers in the U.S.A. who manufactured 1,3-butadiene monomer showed a moderate and significant excess of lymphohaematopoietic cancers (ICD-8 codes 200-209) based on 42 deaths. People employed before 1950 were especially at risk, but there was no convincing association with a cumulative exposure score. Furthermore, a total of 13 leukaemia cases (ICD-8 codes 204-207) only slightly and insignificantly (SMR=1.1, CI 0.6-1.9) contributed to the excess of the lymphohaematopoietic cancers (Divine & Hartman, 1996). A small cohort study of 1,3-butadiene production workers found 2 cases of leukaemia, which was not a significant excess (SMR=1.2, CI 0.2-4.4) (Ward et al., 1996). There have also been reports on a follow-up of styrene-butadiene rubber workers at 8 plants in Canada and the U.S.A. There was a consistent excess of leukaemia and a significant dose response relationship with cumulative exposure to 1,3-butadiene that remained after adjustment for exposure to styrene. Based on 48 leukaemia deaths, the SMR=1.3 (CI 1.0-1.7) (Delzell et al., 1996). When stratified into leukaemia deaths by cumulative ppm-years, the results were as shown in the following table (Macaluso et al., 1996, which overlaps with Delzell et al., 1996).

Leukaemia deaths by Cumulative ppm-years	Observed deaths	SMR	95% CI
0	8	0.8	0.3 – 1.5
< 1	4	0.4	0.4 – 1.1
1 – 19	12	1.3	0.7 – 2.3
20 – 79	16	1.7	1.0 – 2.7
≥ 80	18	2.6	1.6 – 4.1

Thus, the evidence for an involvement of 1,3-butadiene in leukaemia comes from a single large, well-conducted study in the styrene-butadiene rubber manufacturing industry. Data from the two smaller studies of 1,3-butadiene production neither support not contradict the large study; however, even after adjustment for styrene, there were exposures other than to 1,3-butadiene in rubber manufacture that were not accounted for. It is not clear that 1,3-butadiene exposure was indeed responsible for the excess leukaemia cases.

Benzene. There is strong evidence coming from a number of different industries linking high levels of exposure to benzene to an increased risk of developing acute myeloid leukaemia. In contrast, there is no evidence to support a causal relationship between exposure to benzene and the risk of developing multiple myeloma (Bergsagel et al., 1999). The data on acute myeloid leukaemia led the IARC (1987) to classify benzene as a human carcinogen.

Formaldehyde An evaluation of the epidemiological data relating to formaldehyde and leukaemia was recently undertaken (IARC, 2005). Excess mortality from leukaemia was observed in six of seven studies of professional workers (i.e. embalmers, funeral parlour workers, pathologists and anatomists). A recently published meta-analysis for exposure to formaldehyde among professionals and risk for leukaemia reported increased overall summary relative risk estimates for embalmers, and for pathologists and anatomists, which were found not to vary significantly between studies. The excess of leukaemia seen in several studies appeared to be predominantly of a myeloid type. There has been speculation in the past that these findings might be explained by exposures to viruses experienced by anatomists, pathologists and perhaps funeral workers. However, currently there is little direct evidence that these occupations have a higher incidence of viral infections than the general population or that viruses have a causal role in myeloid leukaemia. Professionals may also be exposed to other chemicals, but they have no material exposure to known leukaemogens. Furthermore, the exposure to other chemicals would differ between anatomists, pathologists and funeral workers, reducing the likelihood that such exposures could explain the observed increases in risk.

Until recently, the findings for leukaemia in studies of professional workers appeared to be contradicted by the lack of such findings among industrial workers. However, some evidence for an excess of leukaemia has been reported in the recent updates of two of the three major cohort studies of industrial workers. A statistically significant exposure–response relationship was observed between peak exposures to formaldehyde and mortality from leukaemia in the study of industrial workers in the USA. This relationship was found to be particularly strong for myeloid leukaemia, which was also observed in the study of anatomists and in several of the studies of embalmers. However, in the study of industrial workers in the USA, mortality from leukaemia was less than expected when comparisons were made using the general population as the referent group. This raises concerns about whether these findings are robust with respect to the choice of a comparison group. Leukaemia has been found to be associated with socioeconomic status, and industrial workers tend to have low socioeconomic status. Thus, the lack of an overall finding of an excess of leukaemia in the cohort of industrial workers in the USA might be explained by biases in the comparison between the study and referent populations. The study also failed to demonstrate an exposure–response relationship with cumulative exposure, although other metrics may sometimes be more relevant.

Mortality from leukaemia was also found to be in excess in the recent update of the study of garment workers exposed to formaldehyde in the USA. A small, statistically non-significant excess was observed for the entire cohort in comparison with rates from the general population. This excess was somewhat stronger for myeloid leukaemia, which is consistent with the findings from the study of industrial workers in the USA and several of the studies of medical professionals and embalmers. The excess was also stronger among workers with long duration of exposure and long follow-up, and who had been employed early in the study period when exposures to formaldehyde were believed to be the highest. This pattern of findings is generally consistent with what might be expected if, in fact, exposure to formaldehyde were causally associated with risk for leukaemia. The positive associations observed in many of the subgroup analyses presented in the analyses of the study of garment workers in the USA were based on a relatively small number of deaths, and were thus not statistically stable.

The updated study of British industrial workers failed to demonstrate excess mortality among workers exposed to formaldehyde (Hall et al., 1991). The lack of positive findings in this study is difficult to reconcile with the findings from the studies of garment workers and industrial workers in the USA and studies of professionals. This was a high-quality study with adequate size and sufficiently long follow-up to have had a reasonable chance to detect an excess of leukaemia. The British study did not include a separate evaluation of peak exposures measured, but neither did the study of garments workers in the USA or the studies of professionals. Also, the British study did not examine specifically the risk for myeloid leukaemia, which demonstrated the strongest findings in the studies of garment workers and industrial workers in the USA and in several of the studies of medical professionals and funeral workers.

In summary, it was considered that there was strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. Increased risk for leukaemia had consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers.

Diesel exhausts and fumes. An authoritative evaluation of possible carcinogenic effects of diesel exhausts and fumes did not identify such exposures as risk factors for leukaemia (IARC, 1989).

Tobacco smoke. The IARC (2004) considered that any association of leukaemia with smoking is weak, so that the more valid evidence is likely to be obtained from cohort studies rather than case-control studies. Since death is usually rapidly fatal from acute myeloid and acute lymphoid leukaemia there is little likelihood that cause of death would be wrongly attributed. Only in the case of chronic lymphoid leukaemia is there an appreciable chance that death would be attributed to the disease when it was actually due to an independent, exposure-related condition. The incidence data for leukaemia in general being associated with tobacco smoking are conflicting, although weakly supportive, whereas the mortality data mostly showed small and statistically significant excesses of the order of 30 – 50% among current

smokers. For myeloid leukaemia there is strong evidence for an association with cigarette smoking and the relationship was considered to be causal. Six out of eight sets of data for men or for men and women treated as a single group showed excess relative risks for current cigarette smokers (Doll et al., 1991; Friedman, 1993; Garfinkel & Boffetta, 1990; McLaughlin et al., 1989; Mills et al., 1990; Paffenbarger et al., 1978). All of the excess risks were more than 60% and all were associated with dose-response relationships. The exceptions were the data set of Adami et al. (1998) in Sweden and a small data set of white insurance policy holders in the USA reported by Linet et al. (1991). There was, however, no clear evidence of any risk for lymphoid leukaemia, only two of eight studies provided any evidence of an increased risk associated with smoking and in neither case was the excess risk significant (Paffenbarger et al., 1978; Linet et al., 1991).. Mean and range quantities of benzene, 1,3-butadiene and formaldehyde, respectively in the mainstream smoke of cigarettes, according to the 1999 Massachusetts Benchmark Study, are 76 (28 – 106), 75 (24 – 123) and 50 (12 – 106) μg/cigarette (Borgerding et al., 2000). According to Korte et al. (2000) linear extrapolation from the known effects of high doses of benzene suggests that this may be responsible for12-58% of smoking-induced acute myeloid leukaemia.

In this same, most recent IARC review of the health effects of tobacco smoke (IARC, 2004), nine studies suggest no association between smoking and risk of multiple myeloma. These include six cohort studies and three case-control studies. Only a relatively small cohort study reported an increased incidence of multiple myeloma among former and current smokers and statistically significant trends by number of cigarettes and duration of smoking (Mills et al., 1990).

Epidemiological Studies Reviewed.

In the epidemiological literature on risk of cancer among firemen that has been reviewed, 14 publications were suitable for examination of leukaemia specifically (Table 2). With the exception of Aronson et al., 1994, myeloid and lymphoid leukaemias were not separated. This feature has the potential of biasing risks towards the null, should known leukaemogens be important exposures for firemen. Several other publications did not separate lymphatic from haematopoietic neoplasms. These were not included in Table 2. Almost all studies were small, only the overlapping studies of Burnett et al. (1994) and Ma et al. (1998) having more than 15 cases.

A case-control study by Morton & Marjanovic (1984) found a statistically significant standardised incidence ratio (SIR) of 3.46 for leukaemia**,** while an early cohort study found a non-significantly reduced odds ratio for leukaemia of 0.6 (Williams et al., 1977). Feuer & Rosenman (1986) conducted a proportionality study in New Jersey, 1974 – 1980 to find that there was a statistically significant increase in proportional mortality ratio (PMR) for firemen with leukaemia (4 cases) in the state as compared with police in New Jersey: $PMR_{NJ}p=2.76$ ($p < 0.05$), but not when compared with men in general in New Jersey: $PMR_{NJ}m=1.77$ n.s. or with in the USA: $PMR_{USA}m=1.86$ n.s. There was no indication of a dose response, but with such a low number of cases, this finding has little value.

Heyer et al. (1990) studied a cohort of 2289 firemen in Seattle, WA from 1945 through 1983 by which time there were 383 deaths. There was a statistically

significant excess mortality amongst firemen with ≥ 30 years fire combat experience from **leukaemia**: SMR=5.03 (CI 1.04-14.70) based on 3 deaths. The association of increased leukaemia risk with long exposure did not appear to be confounded by age. The standardised mortality ratio for age < 65 years was, SMR=1.55 (CI 0.42-3.96) based on 4 cases and for age ≥ 65 years, SMR=2.07 (CI 0.43-6.06) based on 3 cases.

Sama et al. (1990) examined associations between fire fighting and cancer incidence in Massachusetts, leukaemia being one of nine malignancies that were studied. Subjects were identified through the state cancer registry files for 1982-86. Disease classification was made on the basis of primary site and histology according to the International Classification of Diseases for Oncology (ICD-O) system (WHO, 1976). Occupation and industry were coded according to the 1980 U.S. Bureau of the Consensus (BC) system (U.S. Bureau of the Consensus, 1982). Male cancer cases included were fire fighter (BC code 417) and fire chief (BC code 413). Two "unexposed" reference populations were used: Massachusetts policemen and white Massachusetts men. Police were selected as a reference group because of their probable similarity to firemen with regard to socio-economic factors. Standardised morbidity odds ratios (SMOR) were increased, but not significantly so for leukaemia among firemen, based on 6 cases, compared with police referents, SMORp = 2.67 (CI 0.62-11.54), but were substantially reduced when Massachusetts white men were used as the reference population, SMORm = 1.12 (CI 0.48-2.59). Incidence data (as used in this study) have the advantage over mortality data in that cancer registry information provides better diagnostic information than death certificates. Over 96% of the cases were pathologically confirmed. Limitations of the study were that occupational information was available for only about 50% of the cases and misclassification of occupation in the cancer registry records could have occurred. Both of these limitations, however, are likely to be random. Another issue is that there was no sub-classification of firemen according to their actual duties, so no assessment of likely exposures is possible. This is likely to dilute effects of exposure and bias risk estimates towards the null, in this study. Thus, the finding of an increased risk in this study is particularly indicative of a possible effect.

Beaumont et al. (1991) calculated mortality rates for 3066 firemen who had been employed in San Francisco, CA between 1940 and 1970. Vital status was ascertained until 1982 and rate ratios calculated using USA death rates for comparison. Amongst 1186 deaths there were 236 cancer deaths, approximately as expected, RR = 0.95 (0.84-1.08). For leukaemia and aleukaemia combined, the rate ratio was lower than expected, but not significantly so, RR = 0.61 (CI 0.22-1.33) based on 6 deaths.

Demers et al. (1992a) studied the mortality of 4546 men employed as firemen in Seattle and Tacoma, WA, and Portland, OR, USA for at least one year between 1944 and 1979. The standardised mortality ratios (SMRs) were calculated using reference rates for the USA as a whole and incidence density ratios (IDRs) were calculated for firemen relative to police in the same cities with standardisation by five-year age groups and time periods. Between 1945 and 1989, there were 1169 deaths in the study population, 291 being cancer deaths. There was no excess risk of overall cancer mortality: IDRp = 0.97 (CI 0.67-1.33), SMRm = 0.91 (CI 0.85-1.07). Also, there was no increased risk of leukaemia either when compared with U.S.A. national rates for men:, SMRm = 1.27 (CI 0.71-2.09) or when compared with policemen from the same cities, IDRp = 0.80 (CI 0.38-1.70), based on 15 deaths. The latter comparison is

likely to be the better comparison, in terms of socio-economic factors that could influence risk. This study, like most others on firemen, relied upon death certificates for cause of death information.

In a study comparing the relative advantages of tumour registry and death certificate information in the U.S. cities of Seattle and Tacoma, WA, Demers et al (1992b) analysed cancer incidence and mortality in a cohort of 4528 firemen and policemen followed between 1974 when all were alive and 1989. For leukaemia (codes 204-208) the standardised incidence ratio (SIR) = 1.05 (CI 0.50-1.93) based on 10 cases and the standardised mortality ratio (SMR) = 1,25 (CI 0.54-2.46) based on 6 cases.

Aronson et al. (1994) conducted a cohort study in metropolitan Toronto, Ontario on all 5414 employees who had worked as firemen for at least 6 months at any time between 1950 and 1989. Deaths and causes of deaths were obtained by computerised record linkage. There were 114008 person-years of follow-up. The average years of follow-up and years of employment were 21 and 20, respectively. The incidence of all cancers combined was not elevated, SMR = 1.05 (CI 0.91-1.20) based on 199 cases. The SMR for lymphatic leukaemia (ICD-9 code 204) was 1.90 (CI 0.52-4.88) based on 4 cases, all of whom were more than 60 years old and with at least 30 years since first employment (SMR=3.51, CI 0.96-8.98). This group analysis almost achieves statistical significance, but the result should be viewed with caution, given the rapid rise in leukaemia incidence with advancing age. The SMR for myeloid leukaemia (ICD 9 code 205) was 1.20 (CI 0.0.33-3.09) also based on 4 cases.

Demers et al. (1994) studied cancer in 2447 firemen in Seattle and Tacoma, WA, USA, with reference to tumour registry data. Incident cancer cases were identified through the population-based registry of the Cancer Surveillance System (CSS) of the Fred Hutchinson Cancer Research Center. Death certificates were not used as a source of cancer information. Duration of active duty was assignable for Seattle firemen and used as a surrogate measure of cumulative exposure to combustion products from fires; no exposure was assigned for years spent in administrative duties or support services. Total years of employment had to be used for Tacoma firemen because records identifying the start and end dates of specific duties were not available for all of them. The study population was followed for 16 years (1974-89) and the cancer incidence compared with that among 1878 policemen from the same cities. There were 244 cancer cases in the study population. There was no excess risk of overall cancer: SIRp = 1.0 (CI 0.8-1.3), SIRm = 1.1 (CI 0.9-1.2) nor was there any excess risk of leukaemia (codes 204 – 208) in particular: SIRp = 0.8 (CI 0.2-3.5), SIRm = 1.0 (CI 0.4-2.1), based on 6 cases. SIRs were also calculated according to duration of exposed employment, but in neither active duty as a fireman (Seattle) nor total employment (Tacoma) was there any underlying relationship of risk with increasing surrogate for exposure. Duration of active fire fighting employment (Seattle) represents an improvement over total duration of employment (Tacoma) as a surrogate index of exposure to specific agents. Thus, there was almost certainly misclassification of exposure in the Tacoma segment, which is likely to bias risk estimates towards the null (as in the Sama et al., 1990 study).

Burnett et al. (1994) conducted a particularly large investigation into the occurrence of cancer death in firemen that was reported as a brief communication (although full details are available from the authors). This was a proportionate mortality study of

white firemen in 27 states of the USA from 1984 through 1990, using data collected from the National Occupational Mortality Surveillance system. There were 5744 deaths, 1636 being due to cancer. The proportionate mortality ratio (PMR) was statistically significantly increased for all cancers combined, PMR = 1.10 (1.06-1.14) and for that portion of the cases who died at < 65 years of age, PMR = 1.12 (1.04-1.21). Deaths from leukaemia were not significantly increased amongst firemen of any age, PMR = 1.19 (0.91-1.53) based on 61 deaths, but were significantly increased for those that died at age <65 years, PMR = 1.71 (1.18-2.40) based on 33 deaths. The strong feature of this study is its very large numbers of cancer deaths. Its weaknesses (shared by other studies of this type) are its reliance on death certificate information, which may be inaccurate, especially for occupation, and give no information on duration of occupation and possible exposures involved, or on possible confounders. In addition, the PMR method of estimating risk will over estimate risk if the overall death rate for the occupational group is low, as might be the case among firemen (DeCouflé et al., 1980).

Ma et al. (1998) used a database overlapping that of Burnett et al. (1994) to examine possible racial differences in susceptibility to cancer mortality. Although the database was extended by three years to 1993, some data were lost because three states were removed from consideration (Alaska, New York and Pennsylvania). There were 6607 deaths, 1817 being due to cancer. Although the stated objective was a racial comparison, there was a large numerical imbalance of deaths between the races. For all cancers combined amongst whites, the mortality odds ratio (MOR) = 1.1 (CI 1.1-1.2) based on 1817 deaths, while amongst blacks the MOR = 1.2 (CI 0.9-1.5) based on 66 deaths. For leukaemia deaths amongst whites, the MOR = 1.1 (CI 0.8-1.4) based on 60 deaths, while amongst blacks there were no deaths from leukaemia. The likely large degree of overlap with the Burnett et al., 1994 study indicates that these cannot be considered as completely independent investigations of leukaemia or multiple myeloma in the white population. This study is subject to the same limitations as described for Burnett et al., 1994.

Bates et al. (2001) studied a historical cohort of all firemen in New Zealand, 1977-1995. Amongst 4221 firemen studied for 58709 person-years **myeloleukaemia** was diagnosed in four cases: SMR=1.81 (0.5-4.6).

Baris et al., 2001 studied an historical cohort of firemen in Philadelphia, 1925 to 1986. From the point of view of measures of exposure, length of the historical cohort and length of follow-up, this was a particularly valuable study. Comparison was made against the general white male population of the USA. The 7789 firemen were normally employed in their late 20s and worked for an average of 18 years, with an average of 26 years follow-up. This provided 204821 person-years of follow-up in which there were 2220 deaths, of which 500 were due to cancer. The measures of exposure that were used were:

1. duration of employment (≤ 9 years; 10 – 19 years; ≥ 20 years);
2. type of company employment (engine only; ladder only; engine and ladder);
3. year of hiring (before 1935; 1935-1944; after 1944);
4. cumulative number of fire runs (low, ≤ 3323; medium, ≥ 3323 & ≤ 5099; high, > 5099, i.e., less than the median, ≥ median and ≤ 75^{th} percentile, and ≥ 75^{th} percentile);

5. accumulation of fire runs (low, ≤ 3191; high, > 3191);
6. fire runs during first 5 years as a fireman (low, ≤ 729; high, > 729), and
7. lifetime fire runs with diesel exposure (non-exposed; low exposed, 1 – 259 runs; medium exposed, 260 – 1423 runs; high, ≥ 1423 runs).

The overall risk of mortality from leukaemia (codes 204-207) was not increased among firemen, with SMR = 0.83 (CI 0.50-1.37) based on 15 deaths. Mortality from leukaemia was not increased among firemen grouped according to duration of employment, cumulative number of runs, number of runs with diesel exposure or year of hiring. However, a high number of runs (> 729) during the first 5 years of employment was associated with a non-statistically significant increase in risk of leukaemia: RR=2.44 (0.70-8.54) based on 9 cases. Work in an engine company was not a risk for leukaemia: SMR=0.28 (0.07-1.12) based on 2 cases, whereas there was an increased among those working in a ladder company: SMR=2.75= (1.03-7.32) based on 4 cases. On the other hand, firemen who had worked in both engine and ladder companies were not at increased risk of leukaemia: SMR=0.98 (0.16-2.62) based on 9 cases. However, since there were only 15 cases of leukaemia, there was limited possibility for sub-group analysis.

Related epidemiological studies

In addition to the studies listed in Table 2, there were other publications on cancer epidemiology of firemen that were examined, but they either did not report lymphohaematopoietic neoplasms of any kind, or did not separate them so that leukaemia could be evaluated. In the latter, Eliopulos et al. (1984) only reported lymphohaematopoietic neoplasms among firemen in Western Australia as a group as a standardised proportional mortality ratio (SPMR) of 1.88 (CI 0.39-5.50) based on 3 cases. Similarly, Guidotti (1993) did not separate leukaemia, lymphoma and myeloma (codes 200-208) in his analysis of firemen in Edmonton and Calgary, Alberta over the period 1927-1987. The combined SMR was 1.27 (CI 0.61-2.33) based on 10 cases. Thus, neither study found a statistically significant increase in their grouping of blood-related neoplasms, but even if there had been an increased risk in a particular category then this would have been more difficult to identify, especially as the numbers of cases were low.

Discussion

1. Problems in the interpretation of epidemiological data.

a. Healthy worker effect.

Fighting fires is a mentally and physically demanding occupation in which burns, falls and crush injuries are commonplace and exposure to smoke and other airborne organic and inorganic substances is part of the job (Gochfeld, 1995). Nevertheless, firemen tend to have a lower mortality rate than the general population, at least during the earlier years of employment. It may be, therefore, that front line firemen are a work population particularly prone to a healthy worker effect, since it appears that many firemen who develop symptoms early in their careers may be moved to other, non-fire-fighting roles (Guidotti & Clough, 1992). This suggestion is supported by the higher prevalence of non-specific respiratory disease amongst firemen who do not actually fight fires (Peters et al., 1974). The healthy worker effect is important during

the earlier years of employment, due in large part to a reduction in cardiovascular disease, but the effect tends to disappear with longer employment (Guidotti, 1995). Any effect in late employment could be due to the removal of workers (because they become unfit) from exposure to risk factors predisposing them to early mortality. Bias of this kind, should it occur, is more likely to affect disease categories other than cancer. In the study of Baris et al. (2001) the SMR for all causes of death was significantly reduced during the first 9 years and after 20 years of employment, but not in the employment range 10 – 19 years. These changes seemed to be largely due to changes in SMRs for circulatory disease and ischaemic heart disease and so they are consistent with the suggestions made by Guidotti (1995

b. Study size

Most of the studies reviewed here are based on small numbers of cases, a characteristic that would have contributed to the lack of consistency amongst the studies. While the two largest studies (Ma et al., 1998 and the overlapping Burnett et al., 1994) had 60 leukaemia and 28 multiple myeloma cases and 61 leukaemia and 34 multiple myeloma cases, respectively, the remainder relied upon 15 leukaemia and 10 multiple myeloma, or fewer, cases. Thus, most of the studies lacked sufficient statistical power to detect a possible moderate association (e.g., a 2-fold increase in risk). The only cohort studies finding statistically significant increases in risk for leukaemia were the proportionality study of Feuer & Rosenman (1986) for leukaemia when compared with policemen in the same state of the USA and the proportionality study of Burnett et al. (1994) for leukaemia cases under 65 years of age
The study of Aronson et al. (1994) is particularly valuable because it did make a distinction between lymphocytic and myeloid leukaemia. Nevertheless, no statistically significant increases in risk were observed for lymphocytic or myeloid leukaemia. Mortality from lymphocytic leukaemia did almost reach significance, particularly when the only four cases were placed as a group amongst those with 30 years or more employment. However, this finding as evidence supporting a hypothesis of causality has no support from what is known or suspected about exposure. Known or suspected occupation-related risk factors for leukaemia are benzene in particular, and then a suspected involvement of 1,3-butadiene; knowledge and understanding of formaldehyde as a risk factor is hardly strong or advanced enough to be considered at this stage.

c. Occupational classification

There have been concerns in several studies based on cancer registry data that information about occupation was missing or that misclassification of the reported occupation could have occurred. The probability of such misclassification is even higher for studies based on death certificates. This is because firemen belong to an occupational group that routinely retires early and then pursues another occupation and it is the last occupation that is recorded; however, it was judged that the effect of such misclassification would be to reduce the strength of the observed association, because it is expected that the misclassification would be non-differential, i.e., it is independent of the cancer diagnosis.

d. Exposure assessment

Generally, few studies could address the issue of actual fire-fighting experience among workers employed as firemen, because a fireman might have been fighting fires, or he might have been assigned purely administrative tasks. Such a lack of sub-

classification could influence risk ratios, biasing them towards the null. In addition, the small numbers of cases available in most studies precluded meaningful analysis according to a fireman's actual or likely exposure.

A general problem affecting studies with firemen is that reliance by the investigators upon the number of years employed as a surrogate for actual exposures at fires probably resulted in misclassification and might not form a sound basis for describing dose-response relationships. Austin et al., 2001a provide such evidence, as only 66% of fire department personnel were in fact 1st line combat fire fighters and many of these combat firemen moved into non-exposed jobs before the end of their careers. In the same study there was a good correlation between the number of runs to fires and the time spent at fires, and they concluded that the number of runs would be a better surrogate for exposure than years worked as a fireman. However, it was also found that the number of runs may seriously over- or under-estimate the time spent at fires for individual crews, so that time spent at fires is the preferred surrogate. In one example, two crews had almost identical numbers of fire runs, but one spent 1.72 times longer at fires than the other. These results are contrary to the opinion of Guidotti & Goldsmith (2002) who specifically do not advise that job assignments or cumulative number of fire alarms to which firemen were assigned be used as measures of exposure (the only practical basis being, in their estimation, duration of employment). Within the studies reviewed here, Demers et al. (1994) used duration of active duty fighting fires and Baris et al. (2001) used not only duration of employment, but also estimated cumulative number of runs and number of runs during the first 5 years as a fireman. The last estimate of exposure was divided into two groups, low and high and the relative risk was greater in the high number of runs category. Year of first employment as a fireman, which was used in several of the studies, is more a measure of latency than exposure, since job categories are likely to have changed over the years. Interpretation of dose-response associations between fire fighting and leukaemia is, however, difficult, taking into account the very small numbers of cases available in sub-group analyses, even when only two categories of exposure were compared.

e. Adjustment for confounders

Most of the studies relied on death certificates as the main source of information and consequently no information about possible confounders (e.g., tobacco smoking and body mass index) was available. An interesting observation is that in two of the three studies (Sama et al., 1990 and Demers et al., 1994) where both policemen and general population males were used as comparison groups, the risk was substantially stronger when policemen were used as the reference population. Policemen would be expected to share many socio-economic factors with firemen and this proximity could make for a more appropriate comparison; however, in the two studies where this was a factor, conflicting results were obtained: Sama et al. (1990) reported a non-significantly higher risk of leukaemia when firemen were compared with policemen, while Demers et al. (1992a) reported a non-significantly reduced risk for a comparison of incidence density ratio (policemen) as compared with a standardised mortality ratio (white men in the U.S.A.).

f. Design weaknesses

Proportional measures can be misleading because their denominator is the total number of cases or deaths from all causes within the same population. The PMR

method of estimating risk, as used by Burnett et al. (1994), will overestimate risk if the overall death rate for the occupational group is low, as might be the case for firemen (DeCouflé et al., 1980). To obtain Mortality Odds Ratios (MOR), as used by Ma et al. (1998), the expected numbers were calculated using all causes of death except cancers from the same occupational mortality database from which the firemen's deaths were obtained. Both PMR and MOR measures rely on death certificate information and is therefore prone to bias because of misclassification of both the cause of death and the exposure. These two studies are interesting, however, because their study populations are overlapping (which should detract from their combined significance) and have used different analytical methods. Nevertheless, they reached different conclusions for both leukaemia and multiple myeloma.

Generally speaking, incidence data obtained from cancer registries form a more reliable and more detailed source of information on which to base analyses (Demers et al., 1992b). In any of these analyses, the characteristics of the reference population is important, it being an advantage to select a reference population whose characteristics are as close to the study population as possible. This advantage was greatest in those studies (Sama et al. (1990); Demers et al. 1992a; 1994) that selected police as a reference group in addition to a more general population.

2. General Discussion

Consistency and the strength of the observed associations are important factors in the identification of causality. No single study can provide definitive evidence for a relationship and the strength of the association (the size of the relative risk) must be taken into consideration.

Two studies that only reported lymphohaematopoietic neoplasms as a group observed non-significant increased risks amongst firemen (Eliopulos et al., 1984; Guidotti, 1993). Of the remaining studies, leukaemia was reported in 14, but there was generally no attempt to sub-classify the diseases according to cell line of origin. Two exceptions were Aronson et al. (1994), who recorded lymphocytic and myeloid leukaemia as separate groups, and Bates et al. (2001), who recorded myeloleukaemia alone. In neither study was risk of myeloid leukaemia increased significantly, but each study had only four cases. Nevertheless, the risk of lymphocytic leukaemia almost reached significance among four cases with ≥ 30 years employment. Of the remaining studies, risk of leukaemia as a whole was significantly increased in just two studies. These were the case-control study of Morton & Marjanovic (1984) and the proportional analysis based on four cases and compared with policemen in the same state of the USA (Feuer & Rosenman, 1986). In addition, Burnett et al. (1994) observed in their proportionality study a significantly increased risk for leukaemia among firemen who died at age < 65 years, but not amongst firemen of any age. Baris et al. (2001) observed a statistically significant increase in risk amongst firemen working in a ladder company, but not if they had worked in both ladder and engine companies.

Problems associated with proportionality studies have been described above. Other problems with the studies under review stem from the nature of the more common adult leukaemia, from job classification and from exposure experienced by firemen in their occupation.

Age-standardised leukaemia incidence increases rapidly with age over about 45 years (see Figure 1). Because of this feature, analysis of data that stratifies cases by either age or years of employment must be done with particular care. Unfortunately, because of the small numbers of cases in the available studies, the desirable fine age stratification must be offset by consideration for the statistical power available. Differences in the age composition of the compared populations could produce biases in the analyses.

Another factor that appears to be associated with different outcomes is whether a fireman has worked exclusively in a ladder or an engine company, or in both. To have worked in both would dilute any effect due to one or other of the work experiences. Firemen assigned to an engine company would be responsible for locating, confining and extinguishing the fire. In structural fires this frequently requires aggressive interior work. During the early phases of a fire, the ladder company would work outside the structure, forcing entry, placing ladders, removing people and ventilating the building of smoke and heat. Later, the ladder company moves inside to search for additional survivors and concealed fires and generally open up the structure. Although it might be assumed that the engine companies will have the heavier exposure by inhalation, this might not be so if the available breathing apparatus is not used all of the time, particularly during overhaul (Gilman & Davis, 1993; Austin et al., 2001a). It is difficult, therefore, to know who has the heavier exposure, but they are assuredly different. One exposure in particular is pertinent to an assessing of leukaemia risks amongst firemen: benzene, a causal agent for acute myeloid leukaemia. In Table 1, the reported concentrations in 9 municipal fires range from 0.12 to 10.76 ppm [0.38 – 34.38 mg/m^3]. Assuming a human ventilation rate of 6 L/min (in the circumstances of a fire it is likely to be higher), this would mean that a fireman at heavy work for 5 – 10 min (Gilman & Davis, 1993) might be exposed to 0.0114 - 0.0228 mg benzene at the low end of the exposure range up to 1.0314 - 2.0628 mg benzene at the high end of the exposure range. The wearing of protective breathing apparatus would reduce this exposure, while the greater physical exertion would tend to counterbalance this effect. Inhalation during fire fighting could, therefore, involve the equivalent of smoking an average of from 0.4 to 181 “light benzene” cigarettes to 0.1 to 19.5 “heavy benzene” cigarettes (based on the Borgerding et al., 2000 Benchmark study) during a single, active knockdown fire fighting phase. In light of this – probably - imprecise calculation, it is likely that fighting fires can be a risk factor for acute myeloid leukaemia, since benzene in cigarettes has been estimated to account for for12-58% of smoking-induced acute myeloid leukaemia (Korte et al., 2000).

In view of the inconsistencies within the available reports, it is not possible to conclude that multiple myeloma arising in firemen is a consequence of their occupational exposures. Furthermore, the lack of any known aetiological factors add to the difficulties in evaluating the available data.

Other important factors in establishing causality are the existence of a biologically plausible mechanism and the demonstration of a dose-response relationship. Currently, there is a lack of a mechanistic basis that could link leukaemia with fighting fires, except for benzene and acute myeloid leukaemia. Because of the generally low numbers of cases the examination of dose-response relationships was not usually possible, although attempts were sometimes made. Baris et al. (2001) examined dose-response relationships in their study population, but there was no consistency in their results: duration of employment showed no relationship, a high

number of runs during the first 5 years of employment reduced the risk and the cumulative number of runs was associated with a significantly increased risk only in the low number category. No separation of acute myeloid leukaemia was available in this study. Given that firemen are exposed to benzene and the effect of benzene seems to be on acute myeloid leukaemia in particular, the lack of sub-classification biases the risk estimates towards the null.

Conclusion

The available epidemiological data in general are not supportive of a conclusion that occupation as a fireman is an unequivocal risk factor for leukaemia. The two available studies that categorised leukaemia according to the cell of origin did not provide reason for arriving at a different conclusion. In the case of acute myeloid leukaemia, however, the exposures might be expected to be a risk factor. This has not been confirmed in the epidemiological studies because breathing protection might be adequate, the studies lack precision (the specific disease was looked for in only two studies), or their statistical power was inadequate. For this disease, although a firm conclusion cannot be reached at this time, larger and more detailed studies might permit a different conclusion.

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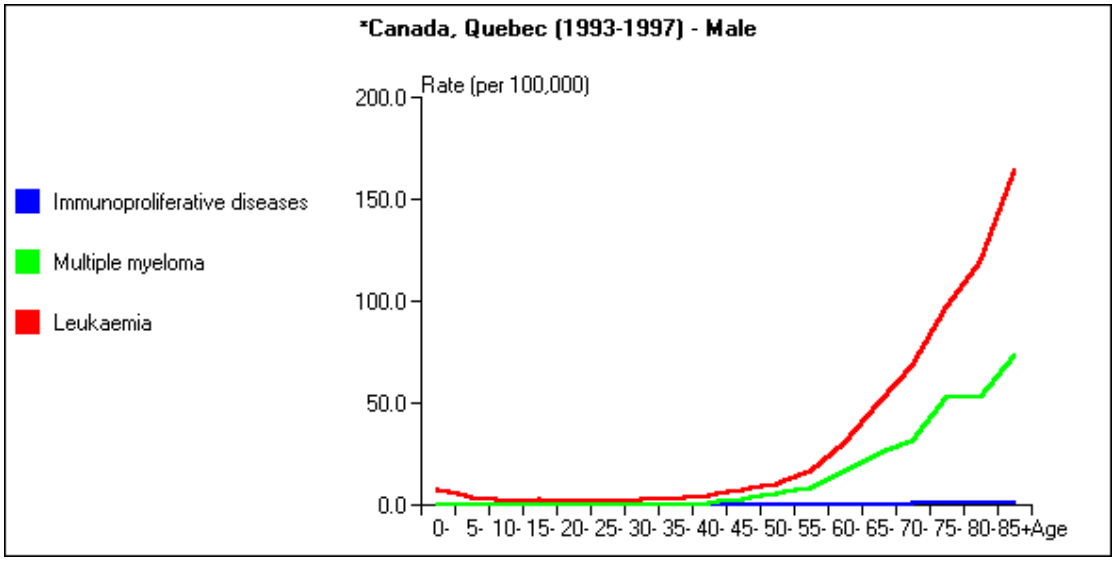
Figure 1. Age-standardised incidences of Leukaemia, Multiple Myeloma and Immunoproliferative Diseases in Males of Quebec and Canada



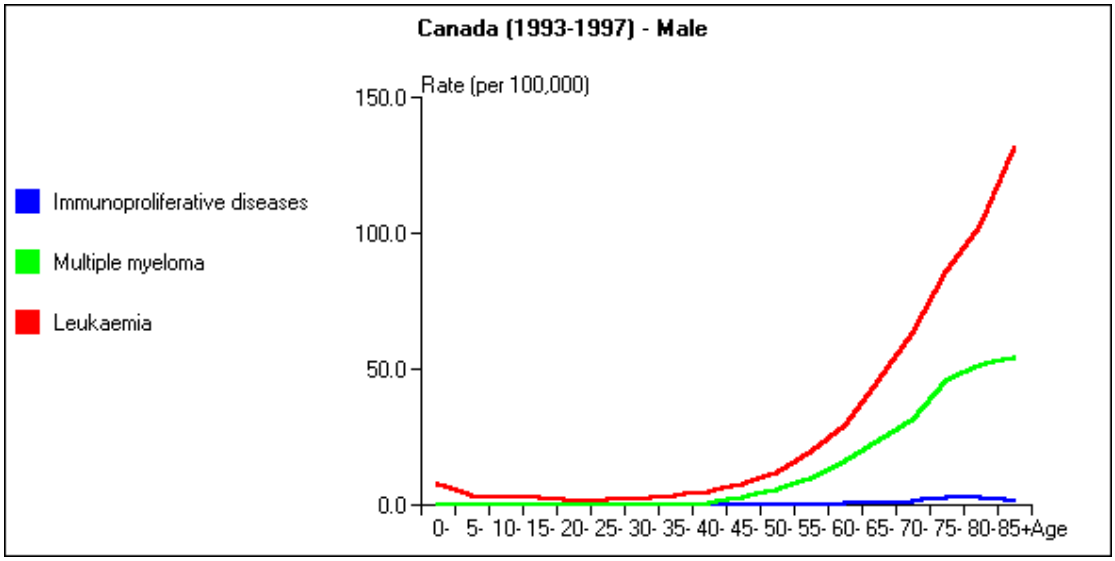


Table 1. Volatile Organic Compounds Consistently found in 9 Municipal Structural Fires (Austin et al., 2001b).

Chemical	**Concentration Range Found (ppm)**
Propene	0.22 – 21.64
Benzene	0.12 – 10.76
Xylenes (*o*-, *m*-, *p*-)	0.06 – 9.19
1-Butene/2-methyl propene	0.03 – 4.08
Toluene	0.05 – 5.52
Propane	0.03 – 3.63
1,3-Butadiene	0.03 – 4.84
2-Methylbutane	0.004 – 0.43
Ethylbenzene	0.01 – 5.97
Naphthalene	0.01 – 2.14
Styrene	0.003 – 2.01
Cyclopentene	0.002 – 3.29
1-Methylcyclopentene	0.001 – 1.79
Isopropylbenzene	0.0004 – 0.55

Table 2. Summary characteristics and results of studies on the relation between occupational exposure as a fireman and cancer

Reference	Study base & type	Reference group	Numbers	Risk* (95% C.I. or significance level)	Adjustments & Comments
Williams et al., 1977	3rd. U.S.A. National Cancer Survey, workers in protection services (firemen, police, etc.). Interviewed 58% of 13179 cancer cases in 8 regions of the USA	Men with cancers at other sites		Leukaemia, OR = 0.60, n.s..	No dose-response analysis
Morton & Marjanovic, 1984	Case-control study of leukaemia in Portland, OR, 1963-77.	Statistical data on occupations for the region.	4 firemen amongst 1678 with leukaemia	Leukaemia, SIR = 3.46 (p <0.01)	
Feuer & Rosenman, 1986	Firemen in New Jersey, 1974-80	NJ police NJ men USA men	No. of firemen not clear. 67 cancer deaths, 4 leukaemias,	Leukaemia, $PMR_{NJ}p$ = 2.76, p <0.05 Leukaemia, $PMR_{NJ}m$ = 1.77, n.s. Leukaemia, $PMR_{US}m$ = 1.86, n.s.	Proportional analysis. No indication of a dose-response
Heyer et al., 1990	Firemen in Seattle, WA, 1945-83.	White USA men	2289 firemen, 92 cancer deaths	Leukaemia & aleukaemia, 7 cases, SMR = 1.73 (0.70-3.58)	Small numbers of cancer cases, resulting in instability of the SMRs. Dose-response analysis inconclusive. 52914 person-years.
Sama et al., 1990	Firemen in Massachusetts, 1982-86	MA police (p) White MA men (m)	315 cancer deaths	Leukaemia, 6 cases, SMORp = 2.67 (0.62-11.54) SMORm = 1.12 (0.48-2.59)	Case-control study of selected cancers from a cancer registry.
Beaumont et al., 1991	Firemen in San Francisco, California, 1940-82.	White USA men	3066 firemen with 236 cancer deaths	Leukaemia and aleukaemia, 6 cases, RR = 0.61 (0.22-1.33)	Analysis of dose-response inconclusive. Number of person years not stated.
Demers et al., 1992a	Firemen in Seattle, Tacoma & Portland, NW USA, 1945-89	Police in the same cities (p). White USA men (m)	4401 firemen with 291 cancer deaths	Leukaemia, 15 cases, IDR = 0.80 (0.38-1.70) SMR = 1.27 (0.71-2.09)	122852 person-years for the 3 cities
Demers et al., 1992b	Firemen in Seattle & Tacoma, WA USA, 1974-89	White men in WA	4528 firemen and policemen. 338 cancers diagnosed; 174 deaths from cancer	Leukaemia. 10 cases, SIR=1.05 (0.50-1.93); SMR=1.25 (0.54-2.46)	Comparison of cancer registry and death certificate information.
Demers et al., 1994	Firemen in Seattle & Tacoma, NW USA, 1974-89.	Police in the same cities (p) Men in the same	2447 firemen with 244 cancer deaths	Leukaemia, 6 cases, SIRp = 0.8 (0.2-3.5) SIRm = 1.0 (0.4-2.1) 0.7 (0.1-2.6)	Sub-group of the Demers et al., 1992b study Small numbers

		counties (m)			
Aronson et al., 1994	Firemen in Toronto, Ontario, 1959-89	Men in Ontario	5414 firemen with 199 cancer deaths	Lymphocytic Leukaemia, 4, SMR = 1.90 (0.52-4.88) With 30 years and more employment, 4 cases, SMR=3.51, CI 0.96-8.98. Myeloid leukaemia, 4 cases, SMR = 1.20 (0.33-3.09)	114008 person-years of follow-up. Dose response analysis non-significant. No information on smoking habits or diet.
Burnett et al., 1994	Firemen in 27 states of the USA, 1984-90	Men who died in the same 27 states of USA	Number of firemen not stated. 1636 cancer deaths	Leukaemia, 61 cases, PMR = 1.19 (0.91-1.53) Under age 65 years, 33 cases, PMR=1.71 (1.18-2.40)	Proportionality study
Ma et al., 1998	Mortality odds ratio study of death certificates of firemen for race-specific cancer risk in 24 states of USA, 1984-93	Men who died from causes other than cancer	6607 deaths of firemen with 1883 cancer deaths (1817 white, 66 black)	**WHITE**: Leukaemia, 60 cases, MOR = 1.1 (0.8-1.4) **BLACK** Leukaemia, No cases	Small numbers for some cancers in whites, small numbers for most cancers in blacks, leading to instability of the MORs.
Bates et al., 2001	Historical cohort study of all firemen in New Zealand, 1977-95	Men who died from cancer in the same period throughout New Zealand	4221 firemen	Myeloleukaemia, 4 cases, SMR = 1.81 (0.5-4.6)	58709 person-years. Results not changed by analysis for 1990-96 period (Cancer Registry database more complete from about 1990)
Baris et al., 2001	Historical cohort mortality study of Philadelphia firemen employed 1925-86	Men in the general USA population	7789 firemen with 2220 deaths	See text for SMRs according to exposure indices. Leukaemia, 15 cases, SMR = 0.83 (0.50-1.37)	204821 person-years of follow-up. Thus, the largest study available to date. Best estimates of exposure because, in addition to duration of employment, the cohort was analysed according to job assignment and – most importantly – number of runs.

*C.I. Confidence Interval

IDR = incidence density ratio; MOR = mortality odds ratio; n.s. = not statistically significant; OR = odds ratio; PMR = proportional mortality ratio; RR = relative risk; SIR = standardised incidence ratio; SMR = standardised mortality ratio; SMOR = standardised morbidity odds ratio; Subscripts: m = men; p = police