Medical Advisory Services
Occupational and Environmental Medicine, Public Health, and Toxicology Consultants

Health Risks and Occupation as a Firefighter

A report prepared for the
Department of Veterans' Affairs,
Commonwealth of Australia

(as represented by the Repatriation Commission)
And the
Military Rehabilitation and Compensation Commission

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EXECUTIVE SUMMARY

This report is prepared for the Department of Veteran's Affairs (DVA) for the purpose of examining the current evidence for risk, and to provide a summary of the current literature addressing the risk, of health outcomes associated with the occupation of firefighting. firefighters. Specifically, the consultant was asked to:

- Conduct a systematic review of the world literature on firefighting
- Highlight aspects of the knowledge base relevant to firefighters at Point Cook
- Address a list of outcomes of primary concern
- Address a priority list of toxic chemicals of primary concern

Conducting this literature review involved the following tasks, performed in sequence and in tandem:

1. Scoping (This step mostly involved preliminary literature searches and review of the newly released NIOSH Study.)
2. Literature search, retrieval
3. Search for grey and secondary literature
4. Review of the literature base obtained for health outcomes
5. Review of the literature base for context
6. Review and interpretation of findings
7. Report preparation and editing

Background

The Royal Australian Air Force base at Point Cook, where an active military firefighting training centre was located, has been the subject of controversy for many years regarding toxic hazards. The site is now decommissioned as an air base. Concern centres on the risks experienced by the military firefighters who trained at the site using fire pits for simulation, the risks experienced by firefighters who responded to alarms on the site and throughout their military career, and identification of outcomes that may be considered for administrative action.

The contract for this assignment committed Building Health Sciences (doing business as Medical Advisory Services) to prepare a report on the world medical literature on firefighting, with special reference to hazards known to have been experienced at Point Cook and concerns expressed by veteran firefighters.

There are basically two ways to approach an issue in general causation which requires one to identify an association (which may or may not be causal). One is to take each of the 286 named conditions and to search the literature for evidence of a causal relationship to firefighting, and the other is to review the entire literature on firefighting and to see which conditions have been recognized as disproportionate in frequency among firefighters and to evaluate them for the plausibility of causation. Both approaches were undertaken in this report. The individual approach was taken for certain priority health outcomes which are discreet and for which the literature supports in-depth investigation. However, the broad literature search has been the primary strategy. The general literature emphasizes municipal firefighters. The RAAF firefighting community is not unlike municipal or civilian aviation firefighters but RAAF firefighters do experience additional exposures based on military aviation and operational requirements, and the use of fire pits in training. These have been taken into account in the conclusions insofar as they were made known to the consultant.

Exposures of concern were also examined, following a priority list of contaminants found on site, which was supplied by Defence. To these were added additional exposures important in exposure of RAAF firefighters. Profiles of these exposures are provided in this report, with detail on their relationship to combustion and the health risk of firefighters. The priority list consisted of about 200 contaminants found in the former fire pits at elevated levels compared to soil at reference locations was also supplied by DVA. Overall, the contaminants found were not surprising and the profile level of contamination was consistent with a heavily polluted industrial site or site contaminated by industrial hazardous waste. It was impractical to provide profiles for each of these contaminants, and unnecessary because authoritative profiles are readily available from many sources.

Exposure

Firefighters are exposed to a number of hazardous chemicals associated with combustion that are known to be toxic. Chief among these are carbon monoxide and cyanide, and, for chronic effects, the polycyclic aromatic hydrocarbons and benzene, and fine particulate matter from fire smoke (which is distinct form fine particulate matter in ambient air pollution). The analysis must therefore go beyond superficial averages and probe more deeply into the evidence. Chemicals encountered in firefighting are particularly significant as toxic agents for cardiovascular and respiratory effects. The most significant for cancer risk are polycyclic aromatic hydrocarbons (PAHs), asbestos, benzene, 1,3-butadiene, trichloroethylene, dioxins and furans, and vinyl chloride; formaldehyde may also be significant. In addition, exposure to exhaust from diesel engines, primarily in the enclosed space of the fire station, adds additional exposures, including nitroarenes. A major change in risk level occurred following the introduction in the 1950's of combustible plastic furnishing and building materials known to generate toxic combustion products which may be carcinogenic. Individual fires may contribute substantial additional exposure, however, such as polychlorinated biphenyl compounds (PCBs). In the military situation, combustion products from JP-4 and JP-8 may be significant.

Although the literature is dominated by studies of the firefighters of the Fire Department of New York who responded to the World Trade Center terrorism disaster on 11 September 200, their exposure does not reflect that of typical professional firefighters. There is emerging evidence that the health experience of FDNY who responded to the WTC disaster is different from that of other firefighters. The present report departs from others in *not* emphasizing the experience of FDNY firefighters who responded in the event, although what can be learned from their experience is discussed when appropriate.

Approach

This review of the literature was intended to identify associations for which the weight of evidence suggests direct causation or an association reflecting causation that arises out of occupation as a firefighter. This does not necessarily imply scientific certainty or proof of causation. For example, a close association between the incidence of a cancer and exposure to a

particular chemical in firefighting (such as benzene, trichloroethylene, or benz(a)pyrene) strongly suggests that either the chemical itself is the causal agent or that it is acting as a surrogate for the responsible chemical (such as another organic hydrocarbon, another chlorinated alkane, or another polycyclic aromatic hydrocarbon) in inducing the cancer. Either way, the risk arose out of work as a firefighter and requires recognition.

The evaluation of cancers associated with firefighting presents methodological and logical problems, a number of them common to other applications of occupational epidemiology. The occupational health problems of firefighters have been extensively studied, to the point that the world epidemiological literature on this topic is among the most complete and detailed available for any occupation. Even so, many issues remain unresolved. This is not a deficiency of the literature. It reflects the inherent limits of applying the science of epidemiology to the framework of claims assessment and eligibility determination (the process of adjudication).

In this report we apply an approach that takes these limits into account in the search for the "weight of evidence" rather than scientific certainty. Essential features of this approach include:

- Heuristic frameworks to describe recurring problems in assessment
- Convergent evidence among studies
- Test for confounding
- Evidence for a threshold effect, as well as increasing risk, with duration of employment or exposure level.

In this report, the guiding principle for evaluation is the weight of evidence, giving priority to human studies but taking collateral evidence into account as needed. The standard employed is not scientific certainty, which is inappropriately stringent in this application, and is also less stringent than would be required for a legislated presumption (evidence for at least a doubling of risk). It should be noted by readers that the alternative to accepting a particular diagnosis as qualification for compensation is not automatically to reject all claims for the condition. If a condition is not recognized as compensable, the alternative is to examine the particulars of the individual case to see if there is a reason to conclude that the condition arose out of work.

Statistical "error" and low power predict that many replicate studies are not likely to show a true excess. Because of power considerations with uncommon disease outcomes and the tendency for misclassification and ascertainment bias to lower the estimate of risk, it is entirely possible by chance alone to miss a true elevation in an uncommon disease. Evidence for an elevation should rightly, therefore, be given more credence than evidence for a negative finding in a similar study, all other things being equal. Meta-analysis has a role, especially in summarizing the tendency of the literature for overall effects, but has its own limitations and cannot rise above the limitations of the studies it pools for analysis.

Recommendations

The following recommendations for recognition of chronic conditions associated with firefighting are offered on the basis of the *weight of evidence*. The alternative to recognizing a particular diagnosis as compensable is to examine the particulars of the individual case.

1. Conditions demonstrating elevated risk among firefighters, weight of evidence sufficient to make a recommendation on general causation:
    - Heart attacks following an alarm or knockdown by up to 24 to 72 hours, resulting in disability
    - Acute respiratory failure and decompensation within 24 hours of an event (toxic inhalation, pulmonary edema), resulting in disability
    - Asthma, irritant induced (associated with a particularly intense event or exposure history)
    - Bladder cancer
    - Kidney cancer
    - Testicular cancer
    - Lymphoma (Diffuse large B-cell lymphoma and follicular cell lymphoma; others unclear and require individual analysis)
    - Leukemia (Acute myeloid leukemia)
    - Brain cancers (Glioma is most likely to be related to firefighting)
    - Lung cancer in a firefighter with little or no smoking history
    - Mesothelioma

- Cancer of the lip
- Breast cancer among males
- Amyotrophic lateral sclerosis
- Noise-induced hearing loss
- Post-traumatic stress disorder and reactive depression (requires compatible history and diagnosis)

2. Conditions for which elevated risk of firefighters is suggested by the current weight of evidence: but which require qualification in a recommendation on general causation

- Accelerated decline in lung function in a non-smoker usually not associated with impairment; history of inadequate respiratory protection)
- Asthma, irritant –induced (sufficient to cause respiratory impairment)
- Chronic obstructive airways disease with minimal or no smoking history (fixed airways obstruction, *not* "chronic obstructive pulmonary disease" as term is generally understood)
- Colon cancer (for individuals with a low *a priori* risk)
- Melanoma (taking into account sun protection, lifestyle, and location)
- Myeloma (overall; cannot differentiate by type at the present time)
- Parotid gland tumours (suggest case-by-case evaluation)
- Nasal sinus cancer (in the absence of other exposures)
- Traumatic injury resulting in impairment leading to disability (must be individualy considered)
- Musculoskeletal disorders (chronic) resulting in impairment leading to disability (must be individually considered)

3. Conditions for which evidence of elevated risk of firefighters is not sufficient to make a provisional recommendation on general causation – individual evaluation is recommended

- Sarcoidosis
- Thyroid cancer
- Esophageal cancer

- Basal and squamous cell carcinomas (taking into account sun protection, lifestyle, and location)
- Laryngeal cancer
- Prostate cancer (below age 60)
- Infectious disease

4. Conditions for which evidence of elevated risk of firefighters is not sufficient to make a provisional recommendation on general causation but association is unlikely – individual evaluation is recommended

- Prostate cancer (above age 60)
- Glomerulonephritis
- Infertility and birth defects in offspring (particular reference to heat exposure during pregnancy)

INTRODUCTION

The health risks experienced by firefighters risks that may lead to chronic impairment and disability has been an active topic of investigation for many years. To address the issue, a considerable body of epidemiological literature has been developed for cardiovascular disease, lung diseases, particular cancers, behavioural disorders, and a few other health problems, with large gaps in between. These issues are part of a broader discussion on the health of firefighters involving health risk, protection of public safety professionals, and equitable compensation.[1-3]

The occupational health problems of firefighters have been so extensively studied that the world epidemiological literature on this topic is among the most complete and detailed available for any occupation. Despite this intense scrutiny over decades, sustained interest and relative completeness of data, there are many unresolved issues, some of which will remain for years to come because statistical certainty is unachievable in practice. Since claims decisions cannot be postponed, many issues involving risk will continue to require resolution by inference and judgment.

Most large studies on firefighters are similar in design and face similar limitations on power for rare outcomes; this characteristic has led to the popularity of meta-analysis as a way to discern trends and certainties. However, the core studies also have their own characteristic strengths, weaknesses, firefighter populations, communities from which they are drawn, timeframes, local patterns of occupational hazard such as housing stock, and methodological nuances, sometimes subtle, that make them different. These differences are valuable because they can be used to drill down to investigate particular issues by examining subgroups, exposure-response relationships, anomalies, and confounding by smoking. The incremental addition of increasingly well-designed, larger, and well-conducted studies on firefighter health has been welcome, even though they do not always provide the same level of detail in analysis as earlier studies.

Meta-analysis has been performed in an effort to overcome some of these limitations,[4-6] with limited success. The experience applying meta-analysis to studies of firefighters has not been satisfactory overall, in our opinion, and this approach does not provide sufficient guidance for individual cases.[7] It is suggested that these issues represent a class of problem in occupational epidemiology that is best approached rigorously by examining the structure of the problem outcome by outcome.

Background

This report was commissioned by the Department of Veterans' Affairs of the Commonwealth of Australia. The primary objective was to provide technical guidance in the identification of health conditions that may plausibly be associated with firefighting as an occupation and so to inform the management and resolution of issues associated with firefighter training and deployment at RAAF Base Point Cook. The secondary objective was to describe the health risk of toxic substances observed to be present at RAAF Base Point Cook or documented by detection at contaminated sites on the base, most specifically in and around burn pits.

The Royal Australian Air Force base at Point Cook, where an active military firefighting training centre was located, has been the subject of controversy for many years. The site is now decommissioned as an air base.

Concern centres on the risks experienced by the military firefighters who trained at the site using fire pits for simulation, the risks experienced by firefighters who responded on the site and may be experienced subsequently throughout their military career, and identification of health outcomes that may be considered for administrative action based on the existing world literature on firefighting and exposure to key hazards.

The contract for this assignment committed Building Health Sciences (doing business as Medical Advisory Services) to prepare a report on the world medical literature on firefighting, with special reference to hazards experienced at Point Cook and concerns expressed by veteran firefighters.

Specifically, the consultant was asked to:

- Conduct a systematic review of the world literature on firefighting
- Highlight aspects of the knowledge base relevant to firefighters at Point Cook
- Address a list of outcomes of primary concern
- Address a priority list of toxic chemicals of primary concern

This report does not address, nor was this project charged with addressing, the following:

- the specific circumstances at RAAF Base Point Cook
- the exposure regime that might have been present historically (intensity, timing, opportunity for exposure, duration, profile of change in exposure, distribution in space, changes over time)
- qualifications for compensation, if applicable,
- individual cases and applications for compensation.

The DVA supplied information to the consultant on the distribution of health issues proposed as outcomes of concern. The complete distribution of 286 named conditions in 440 individual cases by organ system is presented in Table 1. Clearly many of the recognized conditions (the musculoskeletal disorders, for example, have little to do with toxic exposure. Other conditions, particularly cancers of the various organ systems, may now or in the future. (The low number of cancers reported to the DVA to date reflects the age of the population affected. Since older age and a relatively long latency is required before most cancers appear, the ultimate proportion of cancer as an outcome is not established in this population.

Table 1. Distribution of diagnoses (not cases) by organ system.

Organ System	*Number of Diagnoses (not cases)*	*Percentage of total diagnoses (not cases)*
Musculoskeletal	87	30
Skin	37	13
Psychiatric/psychological	35	12
Gastrointestinal	35	12
Ear, nose, and throat	31	11
Neurological and eye	19	7
Immunological, infections, hematological	5	2
Genitourinary	14	5
Endocrine and metabolic	10	4
Cardiovascular	7	2
Respiratory	4	`1
Dental	3	1

The conditions of greatest medical concern include, among cancers, metastatic adenocarcinoma of the lung (suspected bowel origin, making it a gastrointestinal cancer), pancreatic carcinoma squamous cell carcinoma of the tongue, non-Hodgkin's lymphoma and prostate carcinoma; among "benign" conditions motor neurone disease, severe peripheral neuropathy, and Sjögren's disease (an autoimmune disorder). These conditions have been specifically addressed in this report.

There are basically two ways to approach this issue in terms of general causation and to identify an association (which may or may not be causal). One is to take each of the 286 named conditions and to search the literature for evidence of a relationship to firefighting, and the other is to review the entire literature on firefighting and to see which conditions have been recognized as disproportionate in frequency among firefighters. Both approaches were undertaken, the broad literature search being the primary strategy, supported by the individual search by health outcome for the priority health outcomes listed.

Exposures of concern were also examined. A priority list of contaminants found on site was supplied by Defence:

- Firefighter, fire fighter
- Chemical exposure, occupational exposure
- Combustion products (toxicology of)
- Fine particulate matter
- Diesel fuel
- Diesel exhaust
- Jet fuel, JP-4
- Polycyclic aromatic hydrocarbons
- Nitroarenes
- 1,3-butadiene

To these were added additional exposures known to be important in exposure of firefighters that need to be understood in some detail. Profiles of these exposures are provided, with detail on their relationship to combustion and the health risk of firefighters.

A comprehensive list contaminant of contaminants found in the former fire pits at elevated levels compared to soil at reference locations was also supplied. As is usually the case, the contaminants found were numerous, almost 200. Overall, the contaminants found were not surprising and the profile level of contamination was consistent with a heavily polluted industrial site or site contaminated by industrial hazardous waste. It was deemed impractical to provide profiles for each of these contaminants, and unnecessary because authoritative profiles are readily available from many sources, such as the International Programme on Chemical Safety.

Methodology

The following tasks were performed, in this sequence (with overlap or in tandem at the subtask level):

1. Scoping
   - 1.1. Selected searches will be performed on a preliminary basis to determine efficiency or terms and yield. [E.g.: firefighters, cancer.]
   - 1.2. Preliminary review of the October 2013 NIOSH Firefighter Study, because of its importance, methodology, and large size.
2. Literature search, retrieval
   - 2.1. Selection of MeSH terms
   - 2.2. Search databases
     - 2.2.1. PubMed
     - 2.2.2. Web of Science
     - 2.2.3. Cochrane Reports
     - 2.2.4. Google Scholar
   - 2.3. Search of literature
     - 2.3.1. For articles on epidemiology
     - 2.3.2. For articles with substantive content on toxicology of listed chemicals
     - 2.3.3. For articles with substantive content on toxicology of combustion materials, as required
     - 2.3.4. For articles on work practices in firefighting relevant to respiratory disease
     - 2.3.5. For articles on personal respiratory protection in firefighting
   - 2.4. Search on internet and source bibliographies for published literature not in journals (Google, Google Scholar)
     - 2.4.1. Book chapters
     - 2.4.2. Symposia proceedings and other reviewed materials
       - 2.4.2.1. Redmond Symposia
       - 2.4.2.2. International Association of Fire Fighters (IAFF)
       - 2.4.2.3. International Association of Fire Chiefs (IAFC)
       - 2.4.2.4. Public Entity Risk Institute (PERI) annual symposia

2.5. Search for grey and secondary literature
  2.5.1. University theses
  2.5.2. Others to be discovered (inventory to be compiled for future investigators)
  2.5.3. Unpublished reports and "grey literature" (including government sources)
2.6. Query to institutions and selected colleagues
  2.6.1. IAFF
  2.6.2. IAFC
  2.6.3. Society of Fire Protection Engineers
  2.6.4. National Fire Prevention Association
  2.6.5. National Institute for Occupational Safety and Health
  2.6.6. Canadian Centre for Occupational Safety and Health
  2.6.7. Colleagues currently active in this field:
    2.6.7.1. Grace LeMasters, University of Cincinnati
    2.6.7.2. Virginia K. Weaker, Johns Hopkins
    2.6.7.3. Stefanos Kales, Harvard
    2.6.7.4. Sara Jahnke, National Development & Research Institutes, Kansas City Univ. of Medicine and Biosciences
    2.6.7.5. Casey Grant, National Fire Prevention Research Foundation
    2.6.7.6. Kathleen H. Almand, National Fire Protection Association, and Society of Fire Protection Engineers

3. Review of literature base
  3.1. Peer-reviewed, published sources and symposia proceedings
    3.1.1. Quality, methodology
    3.1.2. Population (and relevance to DVA)
    3.1.3. Outcomes addressed
    3.1.4. Data quality and limitations
    3.1.5. Decision whether to exclude from the database
  3.2. Reviewed, secondary sources and grey literature
    3.2.1. As above for quality and data limitations
    3.2.2. Contextual value
    3.2.3. Decision whether to exclude from the database
  3.3. Contextual literature
    3.3.1. For toxicology
    3.3.2. For work practices
    3.3.3. For respiratory protection
    3.3.4. Decision whether to include in the database and cite in report
4. Review literature for context
  4.1. Toxicological principles (e.g. irritant gas exposure and reactive airways disease)
  4.2. Individual toxic agents (e.g. JP-4, trichloroethylene)
  4.3. Exposure assessment (in firefighting)
  4.4. Work practices (e.g. knockdown, overhaul, rescue)
  4.5. Personal protection and patterns of use
5. Review and interpretation of findings
6. Report preparation and editing

Approach to Interpretation

This report is intended to be guidance, not a recipe. The consultant was not given instruction beyond to review of the literature and tformulate recommendations for identifying an elevated risk in the compensation process. This is appropriate because the final decision on which policies to pursue and which health outcomes to recognize is a policy decision, to be made by accountable authority and implemented by informed management, not an agenda supplied by a consultant. It may, for example, be determined that the specific risks of military firefighters deviate from municipal firefighters in ways that render a recommendation or an observation about risk inapplicable. The approach taken, therefore, has been to advise the client, the DVA, on the weight of evidence identifying risks for firefighters in the world literature, to make a preliminary informed judgment of their applicability to the RAAF firefighting population, and to offer recommendations that reflect the limits as well as the certainties of identified associations.

Some of the associations identified suggest an elevated risk for military firefighters based on a substantial contribution to total risk, rather than on the basis that firefighting is the main risk or that occupational exposures drive the risk in the firefighting population. The evidence presented here is guidance for decision makers, with preliminary conclusions on the weight of evidence (balance of probabilities) for an elevated risk, which is the reasonable standard of certainty for deciding on eligibility for compensation. This is not the same thing as identifying evidence of causation by a standard appropriate for a rebuttable presumption, which by definition (for any member of a group, all other things being equal, the outcome is most likely to have arisen from occupation and not from another cause) implies that occupation is the main driver of elevated risk in the population.

Weight of Evidence

The "weight of evidence" is the operative guidance in making the recommendations in this report. The term "weight of evidence" has two distinct meanings in the application of epidemiological evidence to compensation policies. It may refer to the weight of evidence for an *association* or a particular finding, such as an elevated risk for a particular disorder among firefighters. It may also refer to the weight of evidence for a particular disorder arising from occupation (firefighting) in a particular applicant.

Throughout this report, a scientific standard of certainty is still used for reporting the findings of individual studies. The most likely (point) risk estimate (however derived) is presented, together with the confidence interval of the estimate, to describe the limits of 95% certainty. However, the 95% confidence interval is a "scientific standard of certainty", not the preponderance of evidence. These summary estimates apply to individual studies but do not describe the totality of the evidence or the weight of evidence. That would be unrealistic and an unfair burden of proof.

There is no "gold standard" for determining that a given claim arose out of occupation (as a firefighter), as there may be for (some) problems in clinical medicine. In the end, for all but a tiny fraction of health outcomes (such as mesothelioma) the adjudicator cannot know with absolute certainty whether a disabling condition arose from exposure related to occupation or not. Conventional medical evaluation only rarely answers the question definitively for diseases (much more often for injuries), the science of forensic toxicology has taken other directions, and biomarkers have not been developed for this purpose. It must therefore be accepted that with the technology and expertise available today, certainty cannot be achieved in many and usually the great majority of claims by medical means. The better informed and reasoned the causation analysis, however, the more explicit and defensible the judgment and the more likely it will be that the system will adjudicate "correctly".

The more stringent the criterion, the more likely it is that meritorious claims will be denied but the validity of those that are accepted will be more certain. The less stringent the criteria, the better chance a meritorious case has of achieving recognition and compensation but at the expense of accepting more (often many more) non-meritorious claims. Every compensation system faces this dilemma. Although adjudication is slowly adopting new approaches of analysis and what is basically forensics, causation analysis relies on informed medical judgment and expert estimates of most probable association and of apportionment.

Although scientific proof regarding causal associations of firefighting would be ideal, it is unattainable for most health outcomes due to practical limitations. To apply scientific certainty (conventionally defined as >95% certainty, based on the usual "p value") to certainty in these matters is unrealistic and would place an almost insurmountable burden on claimants, because of the limitations and uncertainties of epidemiology, especially, and toxicology and the absence of definitive information for most associations.

More realistic is to search for evidence that the methods described above are satisfied and that they indicate an elevation in the true risk of the actual disease in question, which may be, and often is, diluted by aggregation into heterogeneous rubrics or obscured by low power, inthe case of uncommon outcomes.

In the search for "bright lines" to guide policy in the evaluation of elevations in risk, only one stands out: a doubling of risk among members of the group (firefighters) compared to the reference population (sex-specific members of the community or a similar defined group). A doubling of risk implies in theory, that, all other things being equal, a claimant who applies from a defined population (in this case firefighters) and who conforms to the characteristics of most members of that population, is more likely than not to have had their health condition arise from risks associated with their shared risk factor (in this case occupation another).[7] Mathematically, a risk ratio of two literally means that the risk arising from firefighting equals the risk arising from other risk factors in the population from which firefighters are drawn (the community), and so constitutes an exact balance of probabilities. Evidence for a true elevation of risk as high as a doubling, once evidence for confounding, the potential for bias, and dilution have been taken into account, would ideally be the rigorous policy standard is for presumption. In practice this level of certainty, while more realistic than "scientific certainty", is also a high standard. It is necessary to identify the correct subpopulations to identify a trend and, to apply the evidence to specific causation or rebuttal, the situation that most closely resembles the applicant's situation. This is often difficult.

However, a doubling of risk is not the only basis that can be used to assess the degree of association of a health outcome required to accept it for compensation or to establish a presumption. In addition to implicitly recognizing that occupation is the primary "driver" of the outcome, with other risk factors playing a lesser role, a policy of presumption can be used as a relatively stringent criterion for compensation if a factor, such as occupation, plays an important role and if "but for" the risk factor an individual would not have developed the disorder but that same risk factor is not responsible for at least half of risk (of a particular health outcome) in the population. An elevation in risk that is less than a doubling, but which is plausible on mechanistic grounds and that is shared by subjects in certain situations of common exposure has been used, for example for veterans in the Viet Nam conflict who were exposed to phenoxyacetate herbicides.

A simple elevation of risk is a much less stringent but more attainable and realistic threshold. Simple elevations reduce to an argument over how much excess represents a substantial contribution to risk in the occupation. Simple elevation of risk has also been used to justify compensation guidelines, particular when jurisdictions develop a "schedule" of compensable diseases already known by other means to be related to a particular occupation or when a common disease (such as lung cancer) is known to be elevated in a particular occupation where it appears against a background of community risk. It is also appropriate when diseases are multifactorial in origin and the exposure has made a "substantial contribution" to risk and when "but for" the exposure, the claimant would not have got the disease, regardless of other exposures.

In the US, at least, there are several systems (the system for railroad workers being the largest) in which the criterion is whether the occupational hazard made a "substantial contribution" to overall risk, even if the hazard was not the necessary, sufficient, or sole causal factor. Some systems accept the argument that "but for" the exposure, the claimant would not have developed the condition, even if the risk factor was a relatively small part of overall risk. (For example, asbestos exposure in a cigarette smoker may contribute less risk than cigarette smoking on the basis of straight apportionment, but population studies suggest an interaction and so for a given level of cigarette smoking the risk may be doubled or more; the conclusion is that "but for" the asbestos exposure, the claimant, even though he or she smoked, probably would not have developed lung cancer.) These three sets of criteria lower the burden of proof on the applicant, which is considered reasonable for situations in which causation is difficult or impossible to prove, the cause of the outcome is likely to be multifactorial (which is often the case in cancer), and in which there is a social interest in protecting a group from an assumed risk, such as warriors and public safety personnel.

The formulation of recommendations takes into account the standard of persuasion. In this report, the guiding principle for evaluation is the weight of evidence, giving priority to human studies but taking collateral evidence into account as needed to explain why an outcome for which the epidemiological evidence is not definitive is plausible or unlikely. The standard employed is not scientific certainty, which is inappropriately stringent in this application, and is also less stringent than would be required for a legislated presumption (evidence for at least a doubling of risk).

The alternative to accepting a particular diagnosis as qualification for compensation is not to reject all cases. If a condition is not recognized as compensable, the alternative is to examine the particulars of the individual case to see if there is a reason to conclude that the condition arose out of work.

These are policy considerations for deliberation and decision. This report can only advise on what has been established in the literature.

Causation Analysis

There are two attractive but, in our opinion, simplistic, approaches to interpreting etiological studies in epidemiology when they are applied to causation analysis and qualification for compensation. They lie at opposite ends of an interpretive spectrum.

The first is a "one hit" model, in which any study that demonstrates an association with sufficient strength is considered to be sufficient evidence to accept the disease outcome as occupation-related. The idea is that as soon as one study shows a positive finding, it is first past the post and the outcome must be accepted as compensable. The "one hit" model is too likely to result in a Type I error, in which an association is thought to be true, or causal, but it is not in reality.

At the other extreme is the "model of scientific certainty", in which rigid consistency, absent homogeneity within studies, and doctrinaire conformity to rules. Such rules include an overly rigid application of the Hill criteria[8] and rules used in some approaches to meta-analysis.[5] This model is inappropriate because it is too likely to result in a Type II error, in which something that is truly associated or causal is judged not to be. Occupational health outcomes occur in a real world of uncertainty, confounding factors, community health trends, different populations, changing technology, epidemiological conventions that obscure diagnostic distinctions, inaccurate measurement and misclassification, methodological bias, and limited access to study populations to achieve statistical power. It is too easy to make a Type II error.

The "one hit model" places undue emphasis on findings that might be due to chance variation and therefore places an unsupportable burden on the system of compensation by accepting some claims that are not, in actual fact, meritorious (through no fault of the claimant). The "scientific certainty model" places an unsustainable hardship on the applicant because proof is almost impossible to achieve by an individual claimant. Documentation is also a problem, because

the scientific literature is not geared to assessing individual causation and so often does not provide essential information of make the link. The appropriate methodology, it would seem, lies somewhere in the middle, and involves critical analysis of the problem. That is the analytical philosophy that has guided this report.

Issues of causation in firefighting represent a class of problem in occupational epidemiology that is best approached outcome by outcome using principles of logic rather than advanced statistical techniques. Key to the validity of the methods described in this paper is the essential criterion that it is the weight of evidence, not scientific certainty, that determines the outcome of the case or claim in a legal setting, such as tort litigation and adjudication for compensation benefits.[9]

In order to provide a more realistic analysis for the specific purpose of compensation, not scientific inquiry, we have formulated a series of methods and applied them to cancer risk among firefighters in this and previous studies.[7] They include the following:

- Heuristic frameworks, developed to describe recurring problems in assessment such as the issue of aggregation and dilution described above.
- Convergent evidence among studies for an elevation of "true" risk among firefighters or compelling reasons why an elevation of this magnitude may be obscured through bias or confounding.
- Test for confounding, by determining if there is a stronger association (higher risk estimate) with progressive refinement in exposure assessment or evidence of increased exposure to work-related hazards.
- Evidence for a threshold effect, as well as increasing risk, with duration of employment or exposure level, which for firefighters do not necessarily correlate closely.

Measuring Risk

In this paper, the risk estimates will normally be presented as they were reported in the original paper. SMRs are given to three places, without decimals in the text when they are expressed as percentages (SMR%) but converted to decimals in the table in the Appendix for easier comparison. SMRs may be considered to be equivalent to relative risks. Relative risks are given as decimals, with no qualification. Odds ratios are given as decimals and identified

as such. 95% confidence intervals follow the point estimate, in the usual format (point estimate; 95% confidence interval lower bound, upper bound), as in (RR 1.05; 0.45 – 2.08). The Appendix to this report presents risk estimates for multiple-outcome population studies relevant to cancer.

All epidemiological risk estimates are just that – estimates – and represent the experience of the populations being studied. Uncommon events, such as lung cancer, are subject to chance variation. This is precisely why one derives confidence intervals for the estimates. The power of a study is its ability to detect an elevated risk when there actually is one. One likes to have a power of at least 80% but few studies can achieve even 50% for lung cancer although it is one of the most common cancers and since 1987 the most common cause of cancer deaths for both men and women.[10] This means that a large fraction of studies, without question, miss the true association. This is not an idiosyncratic opinion or controversial: it is inherent in the definition of power, as well as easily observed in practical experience.

Critical to assessing the strength of an association is a measure of risk. The magnitude of risk is expressed in occupational epidemiology in one of two general forms. A cohort study examines the experience of a group of people with a common exposure factor (such as occupation as a firefighter) and compares it with the experience of a benchmark derived from a reference group, preferably a large similar group of people but often the general population. A case-referent study examines how frequently persons who got the disease (the "cases") had the common factor of concern (such as occupation as a firefighter) and compares it with the frequency of that factor in cases that are known not to have the disease at the time of the study (the "referents"). Mathematically, the two are identical for very large populations but operationally they represent two different points of view and are undertaken using different methods.

Cohort studies are used when exposure can be readily documented for a group for which health outcomes can be determined. Cohort studies use a risk statement called the "relative risk", which is often expressed as a "standardized" (age adjusted) mortality or incidence ratio. (For example, such a ratio might be deaths from or new cases of a particular disease in firefighters compared to those in a reference population, usually the general population or sometimes to police.) Case-referent studies are used when the investigator must find the case first and then

reconstruct exposure, usually by a questionnaire or by looking it up in personnel files. Case-referent studies use a risk statement called the "odds ratio", which represents the odds that a case has a particular characteristic or exposure. Because case referent studies usually have smaller numbers of subjects than cohort studies, they are usually less certain statistically and their interpretation is less straightforward.

Studies that observe the experience of a population over time (i.e. cohort or prospective studies) use a ratio of the observed number of cases to the expected number of cases or relative risk (RR). This may be expressed as the ratio, in which case no risk would be 0, risk that is the same as the general population or a reference group is 1 by definition (in other words, unity), risk that is elevated is >1, and risk that is reduced is <1, although a risk <1 is usually interpreted more simply as "not elevated". When referring to the frequency of deaths after adjustment for age, this ratio multiplied times 100 is called the "standardized mortality ratio" (SMR% in this report) and when referring to the fraction of all deaths represented by the particular outcome it is called the proportionate mortality ratio (PMR). (Confusingly, contemporary authors, such as Baris et al.[11] express SMRs as relative risks, without the conventional normalization to 100. Older studies use the percentage convention.)

The alternative term for describing magnitude of risk is used in study designs that compare how often a risk factor was present in the past among those who have developed the outcome and compares that with those who did not (case-referent or retrospective studies) in the form of a ratio. This is called an odds ratio (OR or sometimes MOR, if specifying associations with mortality). The odds ratio is closely related to a relative risk mathematically but generally, as noted, has more uncertainty.

Once the risk estimates are derived, they must be interpreted. A risk the same as the reference group is equal to 1 by definition. A risk estimate greater than unity (RR > 1, OR > 1.0, SMR% > 100, PMR > 100), is an "elevation" in risk. Variability around this estimate is to be expected because of random "error" (which is not "error" in the usual sense of a mistake but random variation or fluctuation by chance). A "confidence interval" is a range of values in which one may be 95% sure, or confident, that the true value lies, within the random uncertainty. An elevated risk may be statistically significant (again, an application of scientific certainty but one which guides interpretation of individual studies) in which case the confidence interval of the estimate of the most likely risk (which is called a "point estimate") clearly falls above

(sometimes, but not usually, below) unity. This applies to an individual study, alone, and is only valid when the study has sufficient statistical power (discussed later) to have a chance of detecting a true result. When numbers are small, elevated risks may not achieve statistical significance simply because the study is "underpowered". This is so common in occupational epidemiology as to be the usual situation for uncommon or "rare" diseases.

The problem is greatest for diseases which are relatively uncommon, compared to others in the population. In statistical jargon, this is called the "rare disease" assumption. (There are actually several usages for this term.) In epidemiology, and statistics, the word "rare" means meaning that the outcome of concern is very uncommon relative to all outcomes, not just in absolute terms, and that the odds ratio approaches the same value as a relative risk. (That is why many of the studies cited in this report treat them as almost equivalent.) The disease does not have to be rare in absolute terms, it must only behave statistically in a way that exerts little influence on the proportion of death or morbidity but is heavily influenced by other, more common conditions in the same population. For example, lung cancer is a very common cancer but because it constitutes less than 7% of all deaths, it would have relatively little influence on the overall mortality statistics of a large population and would be considered "rare" for the purpose of statistical analysis. At the other extreme, heart disease causes more than 25% of all deaths and so would not be considered rare, because changes in heart disease noticeably affects the proportionality of other deaths.

The magnitude of the elevation in risk is as important as statistical significance, especially for "rare" diseases. (The next subsection will elaborate on this statement.) Context is everything. In conventional epidemiology, an elevated risk of (expressed in terms of RR) 1.50 is common and considered unremarkable. However, in the epidemiology of air pollution and fine particulate matter, huge populations and therefore abundant statistical power confirm the significance of relative risks on the order of 1.01. In occupational epidemiology, on the other hand, an elevation below 1.5 is usually not considered strong evidence of an effect because of possible confounding. An elevation above 2.0 is considered to be more plausibly associated with an effect because as the RR increases confounding becomes less likely as an explanation for the apparent risk. Such elevations may or may not indicate true elevations in risk, of course, and so always have to be evaluated individually, on a case-by-case basis, with collateral evidence and by the methods outlined below.

Another way to look at this issue is by the "attributable risk fraction" (ARF), also called the "aetiological fraction". The "attributable risk" of a particular risk factor for a particular disorder is the *number* of cases that are statistically associated with that particular risk factor. This number can be invaluable for planning health services but it is not very useful in epidemiology. A more useful way to express it is as a fraction of the total that can be attributed to the risk factor acting alone, which simplifies conveniently to (RR – 1)/RR. For example, if the relative risk of an exposure is 1.50, then the attributable risk fraction (ARF) is 33% (= 1.50 – 1 / 1.50, converted to a percent). If RR = 1.0, then the ARF is 0, which is another way of expressing that there is no contribution to disease risk from the factor (i.e., it is merely an attribute and not a risk factor). Importantly, if RR = 2.0, then ARF = 50%, which means that risk factor equals the risk deriving from all other risks in the population, which means that the odds are even and therefore the standard of "balance of probabilities" is met.

The ARF applies only to populations. The attributable risk of a particular risk factor is a description of its impact on a population, not a contribution to the risk of any one individual. "Attribution" is an epidemiological term, applicable to populations, not a workers' compensation term. The workers' compensation analogue is "apportionment" but this applies to the proportionate influence of risk factors in individual cases.[50] An ARF may be the best estimate of apportionment in an individual case when the case is exactly or close to the average profile of the population at risk. However, individual subjects may deviate considerably from the average characteristics of the population. Adjudication is (in most Acts) supposed to be undertaken in individual cases.

Sources of Uncertainty

Uncertainties in studies on risk of firefighters come from several sources:

- *Data gaps*. For example, there are no studies of lung cancer risk among nonsmoking firefighters. Such gaps clearly represent questions that have not been addressed, for whatever reason, in studies of firefighters. It is well known and accepted that "absence of evidence is not evidence of absence", as a general proposition. However for other outcomes, "the absence of evidence" may actually be "evidence of absence". This is

because there is a bright spotlight on the profession. Firefighters are a highly visible occupation that has attracted great interest from the public and from scientists, both because of the features of the occupation (toxic exposures, extreme ergonomic demands) and because of convenience and cooperation as research subjects. There has been concerted and intense research on the occupation for five decades. Firefighters are closely monitored, and there has been an atmosphere of strong incentives and even competition for investigators at institutions around the world to study firefighters, even more so since 2001. An uncommon outcomes (such as parotid gland carcinoma) or an elevated risk of a relatively common medical condition (such as peripheral neuropathy) appearing in firefighters would attract attention and be recorded in the scientific literature. This is not to say that nothing could possibly be missed, but it would be unlikely that a major association or consistent and obvious finding would be overlooked in this occupation.

- *Exposure-response relationships*. Very few studies (e.g. Baris et al.[11] and Guidotti[12]) report exposure indicators other than length of service. The absence of exposure information has severely limited interpretation of the literature for important outcomes , such as respiratory disorders.
- *Disease rubrics*. Important distinctions in clinical diagnosis are lost when diseases are put in categories. For example, the leukemias are separate and distinct diseases and at least one of them (acute myelogenous leukemia) is highly associated with benzene exposure. However, the leukemias are almost always put together for analytical purposes (the exception being Aronson/L'Abbe and Tomlinson[13] and reports based on that work). The reason for this practice, which was much more extensive in the past, was that statistical methods work better with larger numbers, but applying improved statistical methods to larger numbers based on illogical combinations can actually obscure important findings.
- *Disease identity (case definition)*. Developing scientific knowledge, particularly about causation, makes many disease rubrics tentative at best. For example, the global consensus on classification of the non-Hodgkin's lymphomas has changed fundamentally at least four times since the 1970's.[14] It is highly likely that certain individual lymphomas are caused by different exposures.[15-17] However, the ability of epidemiology to identify occupational associations with any certainty is weak, because of practical limitations. There are no studies on individual lymphoma types and risk from firefighting.

- *Statistical error*. In statistics, the term "error" does not mean a mistake. Random error means that because of chance, the true value is obscured by random variation. This is a characteristic of every epidemiological study. For rare diseases (using an epidemiological definition) such as cancers, this translates into an inability to be sure whether there is an elevated risk or not. The theoretical argument over whether "positive" studies (which show an elevation) outweigh "negative" studies (which do not) is a major preoccupation of occupational epidemiology. As a practical matter, positive results do matter more than negative studies in the situation of rare diseases and causation, because it is much easier to miss a true association because of bias and power limitations than it is to find a marked but spurious elevation in association appearing in multiple studies, in the absence of a high degree of confounding. The reasons will be discussed in detail in this report.
- *Bias.* In principle, bias (a systematic error, in which the results are affected by some problem in gathering data) can result in an over- or under-estimate of risk. In practice, in etiological epidemiology of rare diseases it almost always results in an underestimate, such that associations are obscured.
- *Confounding*. Many other risk factors affect disease outcomes, most obviously smoking. Almost no studies on firefighters have corrected for confounders (the exception being Beaumont et al.[18]). The most serious source of confounding, however, may be time, because length of employment, duration of exposure, latency (for most solid cancers), and age (and therefore susceptibility to most cancers) are all closely correlated but not the same and there is inevitably insufficient data to disentangle the covariance.
- *Paradigm blindness*. The prevailing thinking in epidemiology is that each study represents the experience of a sample population from a universe of firefighters exposed more or less uniformly (with random variation) to hazards. This paradigm can blind investigators to the differences in generations and eras of exposure, in underlying or "baseline" risk from the comparison populations, and in the reality that populations are collections of individuals, not tangible entities with an independent existence.

Smoking as a Confounder

A confounder, in epidemiology, is a risk factor that is linked to both the risk factor under study and the outcome, so that it interferes with the interpretation of the risk factor under study. The confounding factor, can be fairly described as a true risk factor, but one in which the investigator is not interested and which therefore gets in the way.

Smoking is the major potential confounding factor in epidemiologic studies of firefighters, as it is in many and perhaps most studies in occupational and public health epidemiology. However, it may not have as strong an effect as is usually assumed and is probably less of a problem than in other occupations.

Estimates for occupations identified in the National Health Interview Survey in 1987 to 1994, which would be relevant to chronic disease presenting at the current time, place the prevalence of cigarette smoking among firefighters in the United States then at about 27%. By comparison, law enforcement officers were 32%.[19] Smoking is also declining, apparently faster among firefighters than in the population as a whole. Prevalence in Australia is likely to vary, but a recent study from South Australia suggested a smoking prevalence rate no higher than 10%[20] and within the current Fire Department of the City of New York (FDNY) of only 3.5%[21]. This is much lower than in the past, when smoking prevalence rates were closer to 40%, but reflects overall trends in the population. There has never been documented evidence that firefighters smoke more than the general population and what scanty data exists from the past suggest that they smoked less than other occupations, at least in modern times.

Smoking is linked to many outcomes of interest in firefighting because cigarette smoke is a combustion product and therefore contains many of the constituents, carcinogenic and otherwise toxic, as fire smoke. (The differences between the two, and with air pollution, are discussed in the section on hazards.) As a result, smoking is a particular problem in studying cancers of the lung, larynx, pancreas, and bladder, and in coronary artery disease, chronic obstructive pulmonary disease (COPD), exacerbation of asthma, and peripheral vascular disease.

Cigarette smoke is much richer chemically than lignocellulosic fire smoke (smoke derived primarily from wood and paper), consisting of over 5000 individual compounds, and contains toxicologically active components such as nicotine not present in fire smoke.[22,23] Some of these components, including nicotine, act as anti-inflammatory agents, apparently damping

down the acute irritation and inflammatory response of exposure to cigarette smoke.[24-31] This may explain why fire smoke appears to be more acutely irritating and may also modify the response to fire smoke. The anti-inflammatory effect of cigarette smoke also appears to be highly selective, modulating some immune and inflammatory reactions and not others.

Smoking is inversely associated with socioeconomic class and is more prevalent in some occupations, particularly those that are, paradoxically, either boring (stimulation as a relief from the tedium) or that involve social mixing (partially due to the transactional nature of sharing smokes). Firefighting has both of these characteristics, interestingly, and is considered a working-class, or "blue-collar", occupation, which suggests greater cigarette consumption. However, this was more true in the past than today. Contemporary firefighters tend to be much more educated, more health conscious, and more concerned about smoke effects because of their vocation. Firefighters also enjoy uniquely high status in their communities, so that past social class generalizations do not necessarily apply.

Cigarette smoking is a common habit and therefore often occurs in combination with other exposures that may be harmful to human health to human health, making it a very common and troublesome confounder. However, there are other reasons why smoking is a particularly formidable confounder. Smoking interacts, often strongly, with other exposures so that interactions such as that with asbestos may significantly enhance, or at least modify, the outcome associated with the exposure of interest.

There is also a statistical reason why smoking is a major confounder, which particularly applies to regression studies. Smoking is one of the few risk factors in which it is easy to quantify exposure in the individual case, by number of cigarettes or pack-years smoked. The ability to quantify risk precisely by number of cigarettes smoked per day makes it much harder to determine the contribution of non-smoking risk factors. Because it is based on the accuracy of prediction of one variable by another, regression methodology strongly favors continuous measurement of independent variables, so something that can be measured precisely is weighted more heavily than something that can only be measured crudely. As a consequence, smoking almost always emerges as carrying the greatest weight in the regression.

When information is available on smoking habits of subjects in a study, it is possible to adjust the risk estimates in the analysis. For individuals and for populations, the usual scale of assessing risk is the smoking history, is quantified as "packs per day." Assuming 20 cigarettes

per pack (the US and the United Kingdom standard; there are 25 cigarettes per pack in Canada and Australia) a smoking history equivalent to 20 years at one pack per day (or roughly 16 "Commonwealth" packs is conventionally accepted as associated with an unequivocal risk of chronic health effects.

At the same time, other people in the population smoke, and the reference groups to which firefighters are compared (usually, the general population or sometimes police) have a prevalence of smoking among their subjects as well. The biggest problem in interpretation would come when there is a discrepancy in smoking rates between the study population and the reference population. In the relatively few studies that have been done, the rate of smoking among firefighters has never been shown to be higher (and is usually reported to be lower) than the general population. This means that a health outcome is unlikely to be due to a higher rate of smoking among firefighters, when compared to the general population or a reference group, such as police, which is unlikely to smoke less.

When data on smoking is not available, at least some generalizations can be made. The difference in prevalence would require that rates of smoking be implausibly high the population of interest (in this case, firefighters) in order to explain a substantial elevation of risk (on the order of 50 to 100%) for a smoking-related disease. The section of this report on lung cancer provides a mathematical derivation which, with some manipulation, also demonstrates why differential rates of smoking alone are almost never sufficient to explain a large excess risk for an outcome that is at least doubled in risk in the study population. This principle was first demonstrated by Fletcher and Ades[32], in 1984, in a study of foundry workers.

Latency

Latency is the time that expires between the action of the cause and the manifestation of the outcome. In cardiovascular disease, it might be the time expired between the first injury to the lining of the coronary arteries and the rupture of a plaque or onset of a thrombus that initiates a heart attack (myocardial ischemia). In cancer, it is the time elapsed between initial induction of carcinogenesis and diagnosis of the cancer. Because the onset of carcinogenesis is unknowable, latency in cancer epidemiology is defined as the elapsed time between first exposure to a risk factor (carcinogen) and the clinical manifestation of the disease.

True latency is rarely knowable for cancer, because the action of the cause cannot usually be pinpointed. It reflects the time after the genetic constitution of the cell has been altered that the cell is dormant, then becomes cancerous and finally proliferates by dividing until a cancer appears that is visible, detectable on tests or interferes with function and is discovered. Latency also varies by exposure, with higher exposures tending to shorten the period of time that elapses before the cancer is detectable.

It is generally held as a rule of thumb that the latency period for solid tumours is on the order of twenty years, but this should be understood simply as the most likely or modal latency, the time elapsed before an excess is observed, and not the minimum time required for the tumour to become manifest. Such rules of thumb do not necessarily apply to individuals. Cancers associated with occupational exposures can and do appear well before an arbitrary latency period, although there is usually a minimum imposed by the biology of the tumour and its rate of proliferation. Tissues of the blood-forming organs may have very brief latency periods, on the order of a few years. Latency for bladder cancer, a solid tumour, among workers exposed to aniline dyes in the early 20th century was less than ten years, during an era of high exposure to these chemical carcinogens. A very few cases of mesothelioma, a cancer with a notoriously long latency period of decades in most cases, will appear within ten years of exposure.

Duration of employment is difficult to separate from latency, which, of course, is also confounded by the aging process.

Positive and Negative Findings

Studies of firefighters are generally large and relatively similar to one another compared to other occupational groups but they almost always still have low power for rare outcomes and are by no means identical. Most occupational cohort studies used to evaluate cancer risk look at multiple sites and are designed to have sufficient power for a relatively common outcome, such as heart disease; they are almost never designed for a single cancer, and when there is interest in a particular type of cancer they do not have sufficient power for resolution. Case-referent studies do examine outcomes one at a time but tend to be low in power to detect an association with occupation. Population monitoring studies (such as cancer registries) often have a similar problem and greater problems with misclassification (missing firefighting as the usual

occupation). The approach used in this report depends on a close reading of the individual studies and piecing together a picture on the weight of evidence.

Power is defined as the probability that the true risk will be determined in a study. Power for most studies of rare outcome is very low, especially when they were population studies not designed to identify the outcome as the main finding. The approach of meta-analysis is to overcome problems of low power in individual studies by aggregating the studies statistically, weighted by contribution of information, and determine the central tendency of the risk for all together. This presents other problems, as will be seen.

An epidemiological approach based on a standard of the weight of evidence, or "more likely than not", must accept the preponderance of evidence for an association even when that evidence does not achieve a scientific standard of certainty. This forces a different way of looking at studies with low power for the outcome of interest.

The essence of this approach is that if one believes that power considerations and inherent bias make it more likely that an association will be missed than that one will be revealed, then one must place greater weight on positive studies. This uncertainty over power means that studies that do show an excess risk should carry more weight in adjudication than the evidence of studies that have not demonstrated an excess risk. Studies that show no elevation in risk may simply have missed the excess and convey no information. Studies that show an excess risk, especially if they are consistent and show a dose-response relationship (one important criterion of a true association) are likely to be more useful is assessing the probably magnitude of the true excess risk.

Occupational and environmental epidemiology generally, and studies of individually "rare" diseases, such as cancer by site, in particular share the common and frequent problem of inconsistent findings among studies. What to do about negative studies when there are strong positive studies addressing an association is highly controversial largely because of the tacit assumption that inconsistency and inhomogeneity suggests disorder and lack of clarity when in actuality these attributes are entirely to be expected when there is very low power in rare outcomes. This is an important practical problem. Decisions on cancer prevention, health promotion, workers' compensation, personal injury, and worker protection depend on interpretation of seemingly conflicting studies.

Studies that are similar in design and study similar populations may still yield inconsistent results, with some showing an excess risk and others showing no statistical evidence

of an elevated risk for the same group. Studies that show an excess risk, which are colloquially called "positive" studies, are often viewed skeptically because they are more apt to demonstrate a Type I error (suggesting that some finding is present when it is not), most often because of bias. Studies that do not show an excessive risk, in that they estimate the risk at close to or below unity, are usually, and often wrongly, taken at face value in practice. However, in the situation of low power for a rare outcome, they probably more likely demonstrate a Type II error, most often either because of limitations in power or because of misclassification bias, which almost always results in an underestimate of risk.

In most situations in occupational epidemiology, the number of studies available from which to draw conclusions is small. Very few occupations have been studied extensively and repeatedly using essentially the same methods. The major ones are firefighters and asbestos workers. These occupations can therefore be examined as a body of evidence, rather than as a collection of individual studies. Even so, these studies should never be assumed to be identical, for all the reasons outlined earlier in this report. Trends over time may obviate the relevance of earlier studies in calculating current risk, if only because of differences in exposure profile and the underlying populations.[33]

As a scientific problem, such discrepancies are often considered, and are always described in the literature, as a challenge for further investigation. ("More research is needed" is the usual phrase.) However, assessment of claims for workers whose exposure occurred in the past must as a practical matter be performed with the knowledge that exists today.

All other things being equal (which they never are), positive studies outweigh negative studies in epistemological if not statistical significance. In individual circumstances, this generalization, like all generalizations, may not be true, but the logic of power dictates that when the assumptions are satisfied, the burden of demonstrating that it is not true falls on those who question the association, not on those who place higher value on "positive" studies.

The argument for giving "positive studies" disproportionate weight assumes the following about the set of studies under consideration:

- The individual studies are based on comparable but not necessarily identical populations, approximating a sample of all workers in that occupation, notwithstanding that

firefighters are recruited out of community populations with somewhat different underlying health characteristics.

- The studies are conducted using similar methodology, primarily cohort studies, with near-complete ascertainment of outcomes for subjects.
- There are a sufficient number of methodologically similar studies to reflect statistical variation due to random error on the level of individual studies (in other words, a reasonable estimate of standard error or the coefficient of variation among studies would be possible).
- Bias in the studies, including and especially confounding, is not strong enough to obscure the statistical anomalies at the level of collections of studies.

Practical decisions, especially where matters of equity are concerned, should therefore not be made on the basis of the "preponderance of evidence" considered as the tendency of the majority of studies. This approach will inevitably miss the correct interpretation in this situation. The totality of the evidence should be considered, including possible reasons for divergent results, differences in the populations studied, signs of confounding (such as an increasing relative risk when exposure assessment is strengthened), and consideration of a bimodal distribution of risk estimates.

On a more technical level, it can be argued based on a strict definition of power that meta-analysis systematically underestimate the true risk when studies of low power are aggregated. Studies that have missed the effect entirely and predictably are combined with many fewer studies that did observe the effect. Unfortunately, there is no easy way to know this.

The "Hill" Criteria

Once an association is identified, the next step is to determine whether the risk factor has played a causal role or is merely a statistical association. To do this, epidemiologists commonly use the widely accepted "Hill criteria". They were proposed by British biostatistician Sir Austin Bradford Hill (1965) in a lecture to the Royal Society of Medicine.[8] Unfortunately, they are widely misunderstood and applied as if they were proofs of causation.

The Hill criteria are a set of guidelines (no more than that) for assessing (not determining) whether an association in epidemiology is likely to be causal or to reflect some other relationship (such as confounding or the operation of an ecological fallacy or one risk factor being an indicator of exposure but not the true exposure). The more criteria that are satisfied, the more *likely* it is that the association observed is truly causal. Hill himself repeatedly emphasized, without equivocation, that his criteria were guidelines, not rules and were neither infallible nor proof of causation. The Hill criteria apply only to populations, never individuals, and only when there are sufficient epidemiological studies available to make broad generalizations. Thus, they are essentially useless for a novel or previously unsuspected association. (Hill understood this very well.)

The central question in most occupational epidemiology studies is that of establishing causation. Most people think of causation as a simple matter of cause and effect. However, it is very rare in occupational epidemiology that a single cause results in a single effect. More often, there are many determinants, some of which may have nothing to do with the subject under study (but which may confound the association of others), that may increase or decrease the probability of a given effect, or outcome, which would sometimes occur anyway. For this reason, one speaks of "risk factors" rather than causes or determinants, and one is careful to avoid describing an "association," a statistical relationship between a suspected risk factor and an outcome, as implying causation unless and until one can prove that the risk factor is a cause and the outcome is an effect. The social and behavioural factors that allow the material risk factors to be in place are themselves "causes" at one level and need to be characterized as such. These social and behavioural factors are themselves embedded in culture, the economy, and political life and values.

One example may suffice. One might imagine a naive epidemiologist studying lung cancer and objects in the home, with the intention of finding a determinant that, if removed, would prevent the cancer. The naive epidemiologist would conclude on the basis of a very strong *association* that ashtrays cause lung cancer. However, association is not the same as *causation*; causation is one form of association. The moderately experienced epidemiologist would dismiss the association as irrelevant, because the presence of an ashtray and the outcome of lung cancer are both outcomes arising from the habit of smoking. The sophisticated epidemiologist would recognize that the association between ashtrays and lung cancer is not trivial because it provides information on behaviour: the presence of ashtrays represents a marker for smoking-tolerant behaviour that may represent 1) a family of smokers, 2) a family in which there are nonsmokers

who have become tolerant of the habit, not forcing the smoker to go outside to indulge his or her habit, or possibly 3) a non-smoking family with more permissive attitudes toward smoking among visitors, who place themselves at risk for passive exposure. The ashtray may be the visible manifestation of a behavioural pattern that allows smoking in that home and that behavioural pattern could be amenable to intervention and a pathway to the prevention of smoking.

Some criteria are stronger than others. These criteria are presented in Table 2.[8]

Table 2. The Hill Criteria for Evaluating a Statistical Association as Plausibly Causal in Epidemiology.

1. Strength of the association
2. Consistency among studies, esp. by different techniques
3. Specificity of outcome
4. Exposure precedes disease outcome
5. Dose-response relationship (epidemiologic)
6. Plausibility of a biological mechanism
7. Coherence of chain of evidence
8. Experimental association, esp. dose-response
9. Analogy to similar effect produced by a similar agent

The Hill criteria for accepting an association as causal are not absolute. They are only guidelines, as Hill himself repeatedly emphasized. They need to be understood for their limitations as well as their strengths:

1. The *strength of an association* is a strong criterion; risk estimates elevated by less than 50% (for example, odds rations less than 1.50) are usually considered unlikely to be strongly associated with a single exposure. This rule of thumb is somewhat arbitrary. Massive studies may have sufficient power to identify smaller risks. However, then the issue arises as to whether that risk is ultimately significant, in a biological or public health sense.
2. The criterion for *consistency* is a strong criterion. Contradictory results from a similar study or an analysis using different approach in the same study calls the original

observation into question, unless there is a good explanation. There are two tendencies at play here. The first is that, in science, falsification is the essential process: we look for the contradiction. The second is that when studies have low power, it is unlikely that a finding will be repeated, exactly, in a second study, although a trend may be evident with a sufficient number of unbiased studies through meta-analysis. This is one reason why "positive" studies are more persuasive than "negative" studies of rare outcomes, such as cancer.

3. *Specificity*, meaning that a single cause produces one or a small number of specific effects in all cases, is the weakest criterion of all. A single exposure (e.g. asbestos) may lead to a number of outcomes (e.g. asbestosis, pleural disease, lung cancer, mesothelioma, colon cancer, and small airways disease). Hill obviously meant this criterion to mean that exposure to a particular agent should be associated consistently with a specific outcome, not that an exposure should be associated with only one outcome, although this is how this criterion is commonly misinterpreted.
4. The *temporal relationship* is essential. Cause must precede effect. Likewise, sufficient latency must elapse for outcomes that require an attenuated or multistage process. This is really the one absolute criterion in the lot.
5. The *biological gradient of exposure and response* is very useful and compelling when it appears. In general, with increasing exposure, the effects should be more frequent and often more severe. This is an important, even defining criterion in environmental epidemiology. It is also essential in risk assessment. However, it is not absolute. Stochastic processes, such as cancer, immune responses, infection, and most reproductive health effects (including pregnancy, after insemination) do not get worse when exposure is greater. They only become more frequent. Toxic effects of a more traditional mechanism become more severe as well, which may push incident cases from one case definition into another.
6. *Biological plausibility* is a strong criterion suggesting a real cause-and-effect relationship. However, the field of biomedical sciences is littered with the skeletons of theories of pathophysiology that were not correct. It is probably more useful to say that when a biologically plausible mechanism exists, an association is more likely to be causal, but that failure to demonstrate a mechanism does not disprove causation.

7. *Coherence of evidence* is a strong criterion. The entire picture should make sense. Coherence is never a feature early in a line of investigation, until there are sufficient studies and observations to cohere.
8. *Experimental or collateral validation* is very strong when such information is available. However, many cause-and-effect relationships are still hard to prove in the laboratory. The classic example has been the carcinogenicity of arsenic.
9. *Reasoning by analogy* is one of the weaker criteria. It is similar to the criteria for coherence of evidence and for biological plausibility. If a similar association has been seen before and proved to be causal, then a cause-and-effect relationship is more likely. However, mere analogy is circumstantial: empirical evidence trumps it every time.

Epidemiology can inform the discussion of risk for an individual but it cannot define it. The methods of epidemiology apply to populations, not small groups or individuals. An estimate derived from an epidemiological method is only an estimate of the value for any individual, and a poor estimate unless the individual closely matches the group characteristics. For example, the risk of lung cancer in a population is an overall rate, presumably adjusted for age. It is a poor estimate for someone who does not smoke, someone who does, someone who is very young, and someone who is very old.

Epidemiology has enormous power, in the epistemological sense of explaining things, because it is a science of generalizations. Epidemiology also has distinct limitations when applied to the individual case, precisely because it is a science of generalizations.

OTHER FIREFIGHTERS

Municipal firefighters have been the subjects for the studies that are the basis for most of this report. It should be clear, however, that this is not the only type of firefighter at risk of work-related health problems. There are three major categories of firefighters relevant to exposure and therefore health risk:

- municipal firefighters (professional or volunteer)
- industrial firefighters (who provide fire and rescue services in facilities such as mines, refineries, and chemical plants; this group most closely resembles military firefighters)
- wildfire (forest fire and brush fire) firefighters.

The remainder of this report deals almost exclusively with municipal firefighters, with one exclusion. World Trade Center responders are examined separately, in this section, because their exposure regime was unique, quite unlike other municipal firefighters.

Industrial Firefighters

The literature is most thin for industrial firefighters, who vary by industry and level of preparation. However, aviation firefighters, particularly in a military command, are more similar to industrial firefighters.

Although they are less often called out, industrial firefighters maintain levels of fitness comparable to professional community firefighters.[34] There is often a high level of pride in their designation, which gives these firefighters status within their facilities and primary occupation.

Industrial firefighters, in addition to being exposed to the hazards of firefighting, have characteristics similar to the industry in which they work and, because they usually work on a voluntary basis, share exposures with production employees. What little peer-reviewed literature there is on industrial firefighters emphasizes fitness and work capacity. The literature that is not peer-reviewed is robust but focused on practice and anecdotal reports. Within the industry, there is a high level of awareness that industrial firefighters are a distinct group, large in number (approximately 1 million in North America), and deserving of respect as a profession.

Two groups likely of special interest to the RAAF are aviation firefighters and oil and gas-field (upstream petroleum industry) firefighters. We were not able to find a significant literature on health risks for aviation firefighters as a group. The literature on oil and gas firefighters identifies well-known exposures but even so it is not robust nor are firefighters differentiated from other work groups in the industry.

Wildland Firefighters

In Australia, specialized firefighters who suppress wildfires represent a hugely important subset of the profession, and a stark line of protection for civilians. Their exposure regime, however, is not closely comparable to that of municipal firefighters or of military and industrial firefighters. Exposure to burning wood (and presumably brush) is chemically simpler and toxicologically likely to be less carcinogenic than burning structures. Health outcomes for wildland firefighters have not been studied as often or as extensively of using the same analytical methods as for municipal workers. Wildland firefighters will therefore not be considered in this report. Reference will be made to them only when there is a particular point in which the literature is relevant.

World Trade Center Responders

There is a large and compelling literature on the health experience of responders to the World Trade Center (WTC) disaster on 11 September 2001 and also the experience of New York City firefighters, both WTC responders and others. However, a close examination of this literature demonstrates that the experience of WTC responders and of firefighters in the New York City Fire Department (FDNY) was unique and that their health experinece is not likely to be representative of firefighters in general. Thus, FDNY members and WTC responders should not be considered as suitable populations for predicting the health outcomes of firefighters in general.

A brief summary of the WTC responders experience is outlined will serve to demonstrate how different the exposure history this population of firefighters truly is.[35]:

On September 11th, 2001, events at the World Trade Center (WTC) exposed residents of New York City to WTC dust and products of combustion and pyrolysis. The majority of WTC-exposed fire department rescue workers experienced a substantial decline in airflow over the first 12 months post-9/11, in addition to the normal age-related decline that affected all responders, followed by a persistent plateau in pulmonary function in the 6 years thereafter. The spectrum of the resulting pulmonary diseases consists of chronic inflammation, characterized by airflow obstruction, and expressing itself in different ways in large and small airways. These conditions include irritant induced asthma, nonspecific chronic bronchitis, aggravated pre-existing obstructive lung disease (asthma or COPD), and bronchiolitis. Conditions concomitant with airways obstruction, particularly chronic rhinosinusitis and upper airway disease, and gastroesophageal reflux, have been prominent in this population. Less common have been reports of sarcoidosis or interstitial pulmonary fibrosis. Pulmonary fibrosis and bronchiolitis are generally characterized by long latency, relatively slow progression, and a silent period with respect to pulmonary function during its evolution. For these reasons, the incidence of these outcomes may be underestimated and may increase over time. The spectrum of chronic obstructive airways disease is broad in this population and may importantly include involvement at the bronchiolar level, manifested as small airways disease. Protocols that go beyond conventional screening pulmonary function testing and imaging may be necessary to identify these diseases in order to understand the underlying pathologic processes so that treatment can be most effective.

FDNY members involved in the WTC response are also qualitatively different from other firefighter populations, for the following reasons[35]:

- The firefighters involved in the WTC response had all the exposures common to other municipal firefighters with the addition of a complex exposure regime unique to the WTC event quite unlike exposures experienced by other firefighters.
- FDNY members are recruited from a very large applicant pool and have a rigorous preplacement qualifying program. Appointment to the FDNY carries high prestige in the occupation. These factors introduce a potentially strong selection bias at the time of hire that is most likely to be observed in the cardiopulmonary fitness of applicants.

- The FDNY introduced health promotion, fitness, and cardiovascular wellness programs earlier than most other fire departments, which introduces a potentially strong retention bias related to cardiopulmonary status.
- The FDNY itself and three academic-based programs maintain a comprehensive and elaborate monitoring program for WTC responders. This intensive scrutiny introduces a potentially strong screening bias when compared to other municipal fire departments and a very strong screening bias compared to the general population. One indicator of that is that a very large excess "total cancer" incidence has recently been reported for FDNY WTC responders, notwithstanding that sufficient latency for solid tumours has not elapsed since "9-11".

The exact exposure mix experienced at street level and in buildings on the first day of the disaster is not known and never will be. The immediate consequence of the conflagrations that ultimately destroyed the twin towers of the WTC was to create a powerful updraft as heated air from the buildings rose over Manhattan. This carried gaseous components, including volatile organic compounds, and fine dust up and away from the area for several hours, reducing exposure at street level. The collapse of the buildings then contributed a different mix, quite unlike most exposures experienced by municipal firefighters. This was mostly pulverized calcined calcium silicate derived from concrete, which was, as best can be reconstructed, relatively coarse (>10 μm aerodynamic diameter) dust yielding a highly alkaline pH (> 8) in aqueous solution, together with an unknown quantity (because it was not measured) of ultrafine particulate matter which would have quickly dispersed. (Almost all dusts of practical toxicological significance, in general occupational medicine and in firefighting, are acid-forming, not alkaline.) Silica and glass fibres were present, but relatively little asbestos. The dust carried other toxicologically relevant materials, such as metals, including iron (which catalyzes oxidation reactions at the cellular level), chromium, a familiar (and allergenic) contaminant of Portland cement, and, in certain samples, lead. Polycyclic aromatic hydrocarbons would have been generated in abundance but with a different distribution than usual (because of the intense heat of the fire) and the volatile components (including benzene) would probably have dissipated early. The dust was accompanied at street level by a gaseous cloud of unknown composition which rapidly dissipated and which was replaced with focal sources of combustion products

from fires at ground level, among them products of burning jet fuel, which have characteristics similar to ultrafine particulate air pollution derived from diesel fuel. Adsorption of volatile agents onto the dust particles is not known but certain to have occurred and toxicologically significant because respirable dust would carry volatile agents into the deep lung with high efficiency.

There is no counterpart in conventional municipal firefighting to this unusual profile of exposure, although some individual components, such as burning jet fuel, may be present in industrial, aviation, and military firefighting.

The intensity of exposure was also exceptional, since surviving NYPD firefighters entered or were trapped within the plume at its worst, always without respiratory protection (because SCBA could not last long enough for rescue efforts), and did not have adequate respiratory protection available during the extended overhaul phase for, in most cases, weeks. Whether or not the profile of exposure is responsible for the apparent acceleration in decline in lung function and increase in symptoms (most famously but inaccurately "WTC cough") is not clear but probable. Thus, generalization from WTC responders to municipal firefighters should not be attempted at this time. Examination of the WTC responders' experience may, however, lead to hypotheses which can be tested on municipal firefighter cohorts in order to test whether generalization can be supported.

Lessons can be learned from the WTC responder experience, but these lessons must be interpreted. They cannot be considered representative of the experience of all firefighters. Where there do appear to be lessons that can be more broadly applied, WTC responders are mentioned in this report.

CHEMICAL HAZARDS CHARACTERISTIC OF FIREFIGHTING

Firefighting as an occupation involves exposure to many respiratory hazards, ranging from irritant gases (such as phosgene and cyanide, both of which are better known for their acute toxicity, and the higher oxides of nitrogen with more intense heat) and products of combustion (polycyclic aromatic hydrocarbons or PAHs and their nitrogen-containing analogues, benzene, 1,3-butadiene) to incidental exposure to structural components such as asbestos (predominantly chrysotile in North America) and to hazardous materials that may be released due to catastrophic failures (such as polycyclic chlorinated biphenyl compounds or PCBs and their corresponding furans, paraoxons from organophosphate pesticides that may be on site, and various dusts, of which more will be said later) or volatilized (innumerable hydrocarbons, including styrene, benzene, and other compounds more familiar as solvents). These inhaled agents are toxic, to some degree, to virtually every structure in the respiratory tract, from the epithelium of the upper respiratory tract to the alveoli of the deep lung. (It is noteworthy that among the agents specifically listed in this paragraph, even those that are not usually considered to be toxic to the respiratory tract apart from carcinogenicity, such as PCBs and PAHs, have been shown in toxicological studies to have the potential to affect tissues present in the respiratory tract.) Exposure during firefighting has changed over decades, with the introduction of synthetic materials (particularly in the 1970's) bringing to the traditional hazards of structural firefighting (in which wood smoke, which is relatively simple toxicologically, has predominated) a wider variety of potential exposures (including cyanide from nitriles and chlorinated hydrocarbon hazards, such as phosgene, from polyvinyl chloride-containing materials).

Simple exposure models based on the assumption of inhalation as the only route of exposure may not adequate characterized exposures incurred during firefighting. Recent evidence suggests that skin absorption plays a greater role than previously believed and that the route of exposure may change the kinetics and therefore the risk of excretion and metabolism of other chemicals.[36] This is best established for PAHs, which have been demonstrated to be absorbed through the skin sufficiently (about 9-fold) to change the calculated risk of cancer in models (not in experiments). This observation lends credence to the frequent observation that mixtures and combinations of exposure may change ultimate effects.

Table 3 is a list of exposures, including combustion products, known to be encountered in firefighting. Individual sections in this report discuss the principal chemical hazards associated with the relevant disease outcomes.

Table 3. Exposures encountered in firefighting.[3,25,37-43]

Exposures encountered during response but not produced by combustion chemistry	Exposures primarily associated with combustion
Antimony (constituent of flame retardant on turn-out gear) *Asbestos* Cadmium Lead PFOA (perfluorooctanoic acid and its product polytetrafluoroethylene) *Pesticides* Polybrominated biphenyl compounds (mixed, low) *Polychlorinated biphenyl compounds* (mixed) Silica dust	Acetaldehyde Acrolein Aldehydes (mixed) Alkanes, straight chain (inc. propane*) Alkenes, straight chain (inc. propene*, 1-butene*/2-methylpropene) *Benzene** Benzaldehyde Brominated hydrocarbons (low) *1,3-Butadiene** Carbon dioxide* Carbon monoxide* *Chlorinated alkanes* (low) Chlorobenzenes (low) Cycloalkanes Cyclopentenes *Dioxins and furans* (including 2,3,7,8-dibenzodioxin and –furan*) Dichlorofluoromethane Ethylbenzene *Formaldehyde* Glutaraldehyde* Hydrogen chloride Hydrogen fluoride Hydrogen cyanide Hydrogen fluoride Isopropylbenzene Isovaleraldehyde *Methylene chloride* Naphthalene (a PAH) Nitriles (mixed) Nitroarenes (analogues of PAHs) Nitrogen dioxide Particulate matter (fine) Phosgene *Polycyclic aromatic hydrocarbons* (mixture, including

	naphthalene*) Sulfur dioxide Styrene* *Tetrachloroethylene* Toluene* *Tricholoroethylene* *Vinyl chloride* Xylenes (including o-xylene*)
Italics indicate carcinogenic potential at levels encountered. "Low" refers to very small detected levels.	* Predominate in nonspecific urban structural fires.

In general, urban structural fires produce more complicated toxic exposures than wildfires[44,45], but the duration of exposure may be longer in fighting wildfires. Fires in industrial facilities where special hazards exist can have unique and potent threats. For example, a fire in a pesticide storage facility containing organophosphate pesticides may be particularly dangerous because of the conversion of these chemicals to the more toxic paraoxon form.

Firefighters are exposed to multiple chemicals, both at the same time and in rapid sequence, mostly by the respiratory route but somewhat by skin.[36] For specific health effects, the combination and the timing may be significant, but the complex interactions of these factors are poorly understood.

Fire smoke is not identical to cigarette smoke and wood smoke is simpler than smoke derived from structures containing synthetic materials (some of which also serve as chlorine donors in chemical reactions). Although they share many of the same constituents, in particular the PAHs, there are important differences. Tobacco smoke and fire smoke purely from burning wood ("lignocellulosic" fuel) has only trace amounts of trichloroethylene, a significant solvent chemical associated with cancer risk, and low levels of other halogenated organic compounds compared to fire smoke; structural fire smoke is rich in these halogenated compounds. Fire smoke from wood appears to have low levels of 1,3-butadiene but this carcinogen is elevated in structural fire smoke and in cigarette smoke.

The first of the next two sections deals with specific exposures characteristic of civilian, municipal firefighters, which would be shared by military firefighters. The second deals with exposures characteristic of or unique to the military and known to be present at Point Cook.

Exposures in Common to Firefighting Occupations

Products of combustion exist in two physical phases, particulate matter and gases. However, particles should be understood not as a distinct phase unrelated to gas but as a complex mixture consisting of a particle core onto which is adsorbed other substances, including gases and volatile organic compounds. For example, the polycyclic aromatic hydrocarbons may exist in air as gases (the most volatile PAHs), as part of the matrix of a carbonaceous particle, and adhering to the surface of a particle.

Gaseous combustion products tend to dissipate rapidly, especially in open air, and may be thought of as consisting of four non-exclusive types in terms of toxicological behavior: 1) common combustion products that are benign or effectively inert (carbon dioxide), 2) common combustion products that are that exert their primary effect on the respiratory tract (phosgene, oxides of nitrogen), 3) common combustion products that cause systemic toxicity that are absorbed by the pulmonary route (carbon monoxide, cyanide), 4) toxic air contaminants unique to a particular situation such as hazmat operations or a fire in a production or storage plant (pesticide paraoxons, isocyanates). Of these, the second and third category are of greatest concern in characterizing the characteristic risks of municipal firefighters, but the fourth is critically important in firefighter responders in specific situations, military firefighters (as in the RAAF), and industrial firefighters. In general, combustion products in the gas phase are primarily of concern acutely and at the scene, although they may have chronic sequelae (consequnces). An important feature of gases is that because of contact with the respiratory tract, their penetration to the lower lung, where pulmonary edema may occur, is governed almost completely by solubility in water.

The role of particles is essential to understand. Particulate matter from fires is carbonaceous, derived almost entirely from burning organic matter. Carbonaceous particulate matter is both a primary combustion product with its own effects (as soot or fine particulate matter) and a carrier of solid, gaseous, and potentially liquid-phase contaminants, such as solvent chemicals (which may also be in vapour form at the fire scene), polycyclic aromatic hydrocarbons, and nitroarenes.

The most important characteristic that defines the behaviour of particles is their size. Larger particles tend to deposit in the upper airway and are removed before they penetrate into

the deep lung. Smaller particles are capable of making their way to the deep lung and the smallest particles can even penetrate lung tissue and pass into the circulation. Generation of particulates from fire smoke has known characteristics. Fires with visible flames tend to produce smaller-sized (or "fine") particulate matter than smoldering or charring fires without flames, a reflection of the less efficient combustion process. The finest particles come from polyurethane foam as fuel, but this was an anomaly. Overall, synthetic materials generate larger particles than wood, although they burn at higher temperatures. Particles generated by both flaming and non-flaming fires may aggregate into larger particles with time.[46]

As important as characterizing the fine particulate matter in fire smoke is understanding what it is not. Fire smoke is not the same as cigarette smoke (which is even more complicated and, as noted, contains chemicals, such as nicotine, that act to suppress acute inflammation). Fire smoke in its particulate phase is also quite different from fine particulate air pollution (which is largely sulfate-derived rather than carbonaceous).

Asbestos

Asbestos requires little introduction to citizens of Australia, who are overly and sadly familiar with the serious health hazards of "blue asbestos" (crocidolite). Most of the world literature on asbestos risk, however, deals with chrysotile, which is minerologically very different. However, asbestos seems to derive its toxicity from its fibrous shape, not its elemental content. All forms of asbestos, as well as some other fibrous silicates, are carcinogenic, particularly causing lung cancer and mesothelioma, and cause non-malignant changes in the lung and pleura (lining of the thoracic cavity).

Asbestos is the naturally occurring fibrous form of six very different silicates (silicon and oxygen compounds, with varying metal and water content). It should be noted that the definition of asbestos is not mineralogical: it is commercial, and somewhat artificial. The six forms of asbestos are only the commercially marketed fibrous silicates; there are several others, including erionite, an equally hazardous fibrous silicate that is also naturally occurring but has no commercial use.

Asbestos would be most commonly encountered incidental to fighting fires in older buildings with structural insulation using asbestos products. That asbestos exposure is a problem

for firefighters is now accepted because of the demonstration of high rates of mesothelioma (SMR 2.00; 1.03 – 3.49, SIR 2.29; 1.60 – 3.19), a cancer of the thoracic cavity essentially exclusively caused by asbestos exposure.[47] Suffice to say that it is now accepted worldwide that chrysotile, while less potent than amphibole asbestos, is causally associated with both lung cancer and mesothelioma and with a variety of non-malignant lung disorders. While contemporary firefighters are unlikely to be heavily or repeatedly exposed to asbestos anymore, they are clearly exposed on occasion to this known carcinogen in disintegrating or disturbed structures containing asbestos materials.

Benzene

Benzene is a cyclic (but not polycyclic, because it only has one ring) aromatic (meaning that it has a shared electron structure in the ring) hydrocarbon (meaning that it consists of carbon and hydrogen). It is a known carcinogen, established as a cause of a form of leukemia known as acute myelogenous leukemia (AML) and is suspected of an association with other types of leukemia and with certain lymphomas. It is also a known cause of a form of bone marrow failure called aplastic anemia and is almost certainly a cause of a related but rare condition known as myelofibrosis, both of which are associated with leukemia. Benzene is produced efficiently in combustion of organic material, especially at lower temperatures, and is the leading suspected cause of elevations in risk for leukemia and the coding aggregations that include leukemia.

Benzene is considered a highly specific carcinogen, in that the only cancer that it has been proven to cause unequivocally is AML. Some studies suggest a role as a cause of chronic myelogenous leukemia (CML) but it is not clear and this would be surprising because CML is a very distinct disease; it is not a chronic form of AML.

Recent recalculations of cancer risk associated with benzene suggest that it is even more potent than previously realized. Latency can also be quite short for cancer and is variable, on the order of months, with intense exposure, to many years. This is explained by the peculiar biology of the bone marrow, which is constantly producing blood cells, and which easily forms clones of transformed cells when production is suppressed.

1,3-Butadiene

1,3-Butadiene is an organic compound produced by combustion that is present in fire smoke, cigarette smoke, diesel exhaust, and air pollution. It is well known and extensively studied because it is also a feedstock, used in large quantities together with styrene, as a polymer in synthetic rubber used in the manufacture of tires, and as a polymer together with acrylonitrile to for nitrile materials. Although 1,3-butadiene is hazardous, the polymers are quite safe and the butadiene-styrene polymer is even used in chewing gum.

1,3-Butadiene has been repeated studied and re-evaluated, in part because human and animal studies have been difficult to reconcile and in part because better controls combined with the decline of the tire industry has limited the population of human subjects available for study.

1,3-Butadiene is highly chemically reactive (because of the double bond) and has long been considered a known animal carcinogen, which led to studies that finally identified it as a probable human carcinogen. IARC classifies it as a category 1 (sufficient evidence) human carcinogen for leukemia. It is also suspected of causing lung cancer and lymphoma (not identified down to type). 1,3-butadiene is also known to be genotoxic and causes reproductive effects in animals due to gonadal atrophy, but the relevance of this to humans at typical exposure levels is not clear. An older observation, which may reflect increased exposure in the past, is that butadiene was associated with accelerated atherosclerotic heart disease in the synthetic rubber industry, where exposure occurred in tire manufacturing.

Carbon Monoxide

Carbon monoxide (CO) is a colorless, odorless, and nonirritating gas that is heavier than air and generated wherever there is combustion with a rich fuel-to-air ratio and oxygen deprivation, such as a smoldering fire or a low flame. It is heavier than air and is particularly dangerous in confined spaces, where it may accumulate to high concentrations. Firefighters sustain significant exposure from carbon monoxide, the characteristic product of incomplete combustion.

Carbon monoxide is the most common cause of environmental poisoning worldwide, including developing countries. It presents a particular and well-recognized hazard for firefighters.

Depending on the circumstances of the fire, firefighters may experience significant inhalation of carbon monoxide and if self-contained breathing apparatus is not used, this sometimes reaches toxic and even fatal levels. Carbon monoxide is directly cardiotoxic because it interferes with oxygen delivery to the heart muscle (myocardium), which is the highest oxygen-consuming tissue in the body. Oxygen requirements of the heart muscle (myocardial oxygen demand) is particularly high during periods of exertion, accelerated heart rate, and depleted blood volume (as by dehydration), all conditions that are common during fire suppression. Carbon monoxide exposure is known to precipitate heart attacks (myocardial infarction) by direct means and, less often, may do so as well by inducing coronary artery spasm.

Non-smoking adults normally have carboxyhemoglobin levels at about 1 percent and develop symptoms when their levels rise, variably, above approximately 5 percent. Heavy smokers may not feel symptoms and may perform normally with levels of 5–10 percent, at which non-smokers would demonstrate cognitive impairment on neurobehavioral testing. Tolerance to higher carboxyhemoglobin levels renders smokers less susceptible to the effects of CO, at least at lower concentrations.

CO is a particular hazard in fires, as a product of incomplete combustion, and therefore represents hazard to firefighters and fire victims. (In such cases, the possibility of concomitant cyanide toxicity should always be considered, as well.) CO, once inhaled, passes efficiently across the alveolar-capillary barrier and binds to hemoglobin quickly and almost completely. A consequence of the high affinity of CO for hemoglobin is that, over time, the level of carboxyhemoglobin rises with continued exposure as it is accumulated at the expense of oxygenated hemoglobin. CO then both prevents oxygen from occupying the binding site and, by a different mechanism, interferes with the release of oxygen at the level of the tissue. This reduces the capacity of blood to deliver oxygen to tissues. The net effect is progressively less oxygenation of tissues with increasing accumulation of CO in the form of carboxyhemoglobin. The result may be cardiac ischemia in persons with preexisting coronary artery disease; these changes may occur due to CO alone above 30 percent carboxyhemoglobin. Induction of angina and increased frequency and complexity of arrhythmias have been demonstrated at levels as low

as 6 percent in subjects with coronary artery disease. Thus, one of the most serious health effects of even low-level exposure to CO is the risk of angina, ventricular arrhythmia, and possibly myocardial infarction in workers who may have silent or diagnosed coronary artery disease. Sudden exposure to very high levels may be fatal in minutes with no warning, due to chemical asphyxiation.

Duration of exposure is as important as the level of exposure to CO because carboxyhemoglobin accumulates over time. High blood concentrations may occur as easily with prolonged exposure to low levels as to transient exposure to moderately high levels. Ventilation patterns also play a role in the exposure; higher minute ventilation results in increased accumulation. Significant elimination of CO occurs only when the atmospheric levels are low. Inhaled CO follows a strict mass effect: the amount of CO in the body is determined, when the atmospheric concentration is elevated, by the product of concentration in the air, ventilatory volume (not rate) over time, and duration of exposure. Nothing else affects the determination.

Cyanide

Cyanide (CN) is a colorless gas that is lighter than air and is perceived by those with the genetic capability to smell it to have an almond-like odor. In fires, it exists as the gas hydrogen cyanide. Hydrogen cyanide is released as a product during the combustion of plastics (particularly nitriles) and natural polymers, including silks, wool, and cotton. Hydrogen cyanide enters the body by inhalation and from the lungs passes into the bloodstream quickly. It is distributed rapidly throughout the body.

Symptoms of acute cyanide poisoning include seizures, coma, respiratory arrest, and cardiac arrest, which can occur within minutes after exposure to moderate to high concentrations of cyanide. Exposure to moderate to high concentrations of cyanide can cause loss of consciousness in seconds, and respiratory depression and cardiac arrest can follow within minutes.

CN is thought to cause toxicity by inactivating mitochondrial cytochrome oxidase, which is critical for cells to derive the energy needed to stay alive. Cell death occurs because cells are unable to extract and use oxygen from arterial blood in energy metabolism. The heart, brain, and

liver are particularly vulnerable to CN poisoning because of their high oxygen requirement. CN is also highly irritating to mucous membranes and causes eye and throat irritation.

Diesel Exhaust

Combustion of diesel fuel in a diesel engine takes place at high temperatures and under high pressure. Emissions are therefore low in carbon monoxide, high in oxides of nitrogen, favoring formation of relatively simple hydrocarbons, and variable, depending on the fuel, in sulfur oxides which are subsequently transformed in the atmosphere to sulfate. Therefore, fresh diesel exhaust is a complex mixture coming out of the engine. It becomes even more complex when it has undergone atmospheric transformations, because once released into the atmosphere diesel exhausts "age" and undergo various transformations due to photochemical reactions and aggregation of sulfate particles into fine particulate air pollution. The distinction between fresh diesel exhaust and the aged diesel contribution to air pollution is critical.

Emissions from diesel exhaust present three sets of problems for military firefighters. The primary problem for firefighters in general is with emissions of fresh diesel exhaust when engines are started up in response to an alarm. In the enclosed space of a fire station, firefighters can be exposed to an acute dose. The secondary problem, for the community, is that once airborne diesel exhaust contributes to community air pollution. (This is a broader public health issue, not an occupational problem unique to firefighters.) Furthermore, military firefighters may be exposed to burning diesel fuel used as an accelerant in fire pits, which would be part of a complex mixture formed at suboptimal temperatures that may or, more likely, may not resemble fresh diesel exhaust.

Diesel exhaust, both fresh and aged, is recognized to be carcinogenic and causally associated with human cancer, specifically of the lung, in populations and occupations exposed to diesel exhaust. In June 2012, IARC reclassified diesel-engine exhaust as a Class 1 carcinogen, meaning that there is sufficient evidence to conclude that diesel exhaust causes cancer in humans, drawn from both epidemiology studying exposed populations and toxicology using animal studies. However, this finding was not a surprise. In 1988, IARC concluded that diesel exhaust was *probably* carcinogenic to human beings but the evidence was not completely conclusive.[48] The case is made most strongly for lung cancer but because of the putative

exposure regime, the risk of other cancers are likely to be raised as well, specifically upper airway, kidney, and bladder, which share many risk factors with lung.

The evidence behind this decision has been summarized by the International Agency for Research on Cancer (IARC), a body of the World Health Organization that has as a primary purpose the evaluation of world knowledge to determine cancer risk from exposures to various agents.[49] IARC is essentially universally considered authoritative in the field of cancer research.

It is well established that specific chemicals present in diesel exhaust cause cancer. In addition to many compounds already known to cause cancer, including and especially PAHs and 1,3-butadiene. Nitroarenes (see above) are nitrogenated versions of complex organic compounds called polycyclic aromatic hydrocarbons (PAHs) which are formed by combustion and comprise a mix of organic chemicals, several of them potently carcinogenic. (See above.)

Several developments since 1988 persuaded IARC that the case for the carcinogenicity of diesel fuels had been fully made and was no longer speculative. The most important was the availability of studies on railroad workers, truckers, and underground miners who use diesel-powered equipment. The most important single study was on railroad workers, and showed an excess risk on the order of 1.40.

Despite interest in cancer, few studies are available for human beings on acute respiratory and cardiovascular responses to fresh diesel-engine exhaust, because this has not been seen as a pressing problem. However, it is clear that fresh diesel-engine exhaust has potentially significant acute effects and that small particles have effects distant from the lung and into kidney tissue.

The gas phase of fresh diesel exhaust does not contain the many secondary pollutants that are important in urban air pollution but, depending on running conditions, may be rich in formaldehyde (a potent respiratory and mucosal irritant and upper airway carcinogen) and acetaldehyde.The particle phase of diesel exhaust also has irritant potential and may induce inflammation. Recent subchronic and acute animal studies suggest that fresh (non-aged) diesel-engine exhaust results in relatively mild inflammatory effects.

The particulate phase of urban air pollution is derived in part, and until recent changes in diesel technology, largely from diesel-engine exhaust emissions. Fresh diesel-engine exhaust produces coarse and fine particulate matter, nitric oxide (nitrogen dioxide is a secondary product not present in diesel exhaust), carbon dioxide, some carbon monoxide (much less than gasoline

engines), and oxidized sulfur compounds (sulfur dioxide and sulfates), variable depending on the sulfur content of fuels.

Formaldehyde

Formaldehyde may or may not be a significant risk in firefighting. Although formaldehyde is a known nasal carcinogen in rodents and a suspected lung carcinogen in human beings, being present at high concentrations in cigarette smoke and combustion products, its effect would not be expected deep in the body. This is because it is highly reactive and so interacts immediately with tissues with which it comes into contact. If it plays a role, it most likely contributes to risk in lung cancer risk and possibly the lymphomas.

Nitroarenes

The polycyclic aromatic hydrocarbons (PAHs) are well characterized toxic chemicals om their own right but they also have nitrogen-substituted derivatives that have similar effects and potency as carcinogens. They are a set of nitrogenated products generated most efficiently in diesel exhaust.

Chemically, a nitroarene can be described as a PAH with one or two nitro- groups (NO–) added on the outside. These nitroarenes are otherwise identical to the PAHs in basic structure. For every PAH, therefore, there is at least one and potentially several homologous nitroarenes. Several nitroarenes have recently been determined by IARC to have demonstrated sufficient evidence for carcinogenicity in experimental avenues and therefore possibly carcinogenic to humans (Group 2B): 3,7-dinitrofluoranthene, 3,9—dinitrofluoranthene, 1,3-dinitropyrene, 1,6—dinitropyrene, 1,8—dinitropyrene, 6-nitrochrysene, 2-nitrofluorene, 1-nitropyrne, 4-nitropyrene; a tenth, 3-nitrobenzanthrone, is considered to have imited evidence.[49]

It has long been known that diesel exhaust was rich in PAHs and their corresponding nitro-arenes, several of which are potent carcinogens known or strongly suspected to cause human cancers: lung, skin, bladder, kidney and upper airway (including nasopharyngeal). Mechanistic evidence is also strong or moderate for the carcinogenicity of several of the

nitroarenes, providing a more than plausible chain of causation. The same issues of mixtures and interactions described for the PAHs also apply to the nitroarenes.

The nitroarenes have been recognized as lung carcinogens by the International Agency for Research on Cancer (IARC). The IARC report, which is volume 105 in the IARC monograph series, has just appeared on-line (in 2013) and will be available in hard copy in 2014.

Oxidant Gases

Oxidant gases consist of gas-phase airborne chemicals that have an oxidizing effect chemically in solution (and in tissue) or photochemically. They include nitrogen dioxide (requires high temperatures), nitric oxide (precursor to nitrogen dioxide and produced in vehicular exhaust), phosgene (requires a chlorine source), ozone (rare in fire situations), and a large number of organic and nitrogenous compounds (many related to nitrogen dioxide) that are important in photochemical air pollution but probably not at fire scenes. Sulfur dioxide and the sulphates (which are formed from the oxidation of sulphur dioxide), by comparison, are not an oxidant gases.

The oxidant gases are potent lung irritants and can be very dangerous in special situations, such as confined spaces. Nitrogen dioxide, in particular, is formed at high temperature with increased yield from high temperatures and so is a potential hazard from uncontrolled diesel exhaust, but in practice serious and potentially lethal exposure occurs mostly in hazardous materials situations involving nitric acid. Phosgene is an even more potent oxidant and is implicated in both lung injury and potentially kidney effects. However, concentrations of both of these gases does not reach high enough levels at a typical fire scene to be major hazards.

Particulate Matter (Fine and Ultrafine)

Fine particulate community air pollution has been extensively studied because it is known to be associated with mortality and illness in populations, although the effects on individual is not predictable. Cardiovascular effects of air pollution are associated primarily with fine particulate levels, as a risk factor for cardiovascular mortality. These effects may occur in normal individuals without unusual susceptibility. Respiratory effects of air pollution, particularly

complicating chronic bronchitis, may place an additional strain on cardiac function. In air pollution studies, the lag time for mortality form cardiovascular events associated with fine particulate air pollution persists beyond 24 hours, which is the current criterion for recognizing "heart attacks" as occupational when they occur after a fire. This suggests that the allowable period for accepting cardiac events as related to fire smoke exposure needs to be longer than 24 hours, perhaps about 36 hours.

Combustion in general generates clouds of small particles of varying sizes. The particulate matter of greatest concern is in the "fine" size range, which starts with 2.5 μm (micrometers, or "microns") and gets smaller. ("Ultrafine" starts at 0.1 μm.) Size is important for several reasons. The smaller the particle, the smaller the mass (which is the traditional measure of exposure, or dose) but the count of particles is much more numerous for a given mass and the combined surface area of the particles is much greater. This means that fine particulate matter that is biologically reactive is much more toxic than an equivalent (and, usually, much larger) mass of "coarse" particles, such as soot. In that size range, particles can also easily penetrate the tissues of the lung and enter the bloodstream. As a result, fine particulate matter exerts a toxic effect, particularly on the heart, much greater than its small mass would suggest.

Urban air pollution has a number of similarities with fire emissions, specifically the health risk of particulate matter in ambient air pollution from the combustion of fossil fuels, especially diesel emissions. However, there are also important differences. The mix of sources of combustion products are not the same and the "aging" effect in the atmosphere chemically modifies the airborne chemicals and results in new particle formation.

Urban air pollution involves predominantly pollutants that have "aged" in the atmosphere for a period, usually for hours. The "aging" process in air pollution is important in the particulate phase for agglomeration of larger particles from fine particle nuclei and for increasing adsorption of volatile and aerosolized contaminants and in the gas phase for photochemical processes that lead to secondary pollutants, such as ozone, nitrogen dioxide, and aldehydes. In air pollution, fine particulate matter is also formed from the aggregation of sulfate (formed from the oxidation of sulfur, mostly in diesel fuels) into fine particles. It is unlikely that diesel exhaust in a fire station or from a fire pit would generate sulfate-derived particulate matter because this process takes time.

Emissions from fire smoke are formed at lower temperatures than the usual contribution to community air pollution and involves fresh emission of combustion products and may or may not include sources of metals and chlorine that modify the characteristics of fire smoke. Fine particulate matter in fire smoke consists primarily of carbonaceous particles. These particles carry volatile chemicals adsorbed on their surface and so have toxicity beyond that of the carbon alone. The presence of metals also adds to the toxicity, apparently through the catalysis of reactions that promote inflammation. The characteristics of fine particulate matter generated at a fire scene may differ from that found in ambient air pollution. Studies on this have only begun.

The size distribution of particles is somewhat more complicated than initially described. Ambient air pollution consists of particulate matter in three somewhat overlapping distributions characterized as cut points but best understood as distinct particle populations: coarse (≤ 10 μm aerodynamic diameter, containing the bulk of the particulate mass), fine (≤ 2.5 μm), and ultrafine (≤ 0.1 μm, representing the largest number of individual particles), each of which represents a particular mode or population of particulate matter differentiated by composition as well as size. In other words, size is not only important in and of itself, but as a marker for different species of particles.

The smaller the particle size, the larger the surface area. Because the surface of these particles has a high affinity many biologically active chemicals, surface adsorption is critical to the biological effects of particulate matter. Fine and ultrafine particulate matter have many orders of magnitude greater capacity for binding volatile organic compounds in their surface and delivering them to deeper structures.

Particles in the coarse mode penetrate efficiently to the lower respiratory tract and are efficiently retained in the alveoli. However, they are also large enough to be deposited efficiently on the epithelial surface of bronchi and small airways and are thus likely to have airways effects as well as alveolar effects, mediated in part by macrophage uptake, and systemic effects. Particles in the fine range penetrate to the alveoli efficiently but are less likely to deposit in airways and more likely to migrate from the deep lung into the circulation and adjacent structures through intracellular junctions and through cells.

Ultrafine particles consist largely of aggregated or agglomerated structures of sulfate or nitrate, some with carbonaceous nuclei. These agglomerated particles tend to stick together when they touch, forming larger agglomerates over time. Fine particular matter consists of both

carbon-derived particles, on which are adsorbed volatile and organic materials, and agglomerated sulfate and nitrate ultrafine particles, which build by accretion into the fine size range.Ultrafine particles behave more like gases than particles in their flow behavior and penetration to the deep lung, and migrate relatively freely, with the potential for systemic effects, however, the evidence for significant health effects is weaker than for fine particulate matter.

At the other extreme, coarse particulate matter in community air pollution predominantly consists of dust, particles of crustal origin (basically, very small dirt particles), bioaerosols, and, of interest in this context, carbonaceous particles formed by combustion on which are adsorbed a variety of volatile and organic materials.

The adsorbed chemical species on both coarse and fine particles are biologically significant. The particle forms a carrier with a large surface area onto which are adsorbed many constituents, particularly: volatile organic compounds, polycyclic aromatic hydrocarbons and nitroarenes, metals (particularly transitional metals and iron, which may be proinflammatory), sulfate, and oxides of nitrogen.

Particulate matter in modern urban air pollution is closely associated on a population basis with mortality risk, the risk of cardiovascular and respiratory disease, pneumonia (indicating an effect on susceptibility), emergency room admissions for asthma, and lung cancer risk. These effects, including and especially mortality, are linearly related to the concentration in air of fine particulate matter. (The relationship is not so clear for coarse or ultrafine particles.) Mortality is most apparent in the aged and chronically ill but are also visible in healthy younger populations, which has led to various theories of mechanism. One explanatory theory is that the timing of exposure is critical because people pass into and out of previously unrecognized stages of susceptibility for many factors, including and especially blood coagulability and thresholds for inflammation.

Polycyclic Aromatic Hydrocarbons

The polycyclic aromatic hydrocarbons (PAHs) are a large family of organic compounds, built on multiple (two or more) aromatic rings, hence the equivalent name “arene”. Several of which are known carcinogens (x is used here to indicate various isomers):

- Benz(a)pyrene x = a,e [isomers of benzpyrene; a is much more common]

[redacted]

- Dibenz(x)pyrene x = a,e; a,h; a,l [isomers of dibenzpyrene]
- Indeno(1,2,3 – c,d)pyrene
- Benz(a)anthracene
- Benz(x)fluoranthracene x = b,j,k [isomers of benzfluoranthracene]
- Dibenzanthracene
- 7-H-dibenzocarbazole
- 5-methyl-chrysene
- Acridine(s)

In addition to recognizing individual PAHs as causing cancer in human beings, IARC has long recognized mixtures of PAHs, such as appear in fire smoke, to be carcinogenic. The significance of recognizing mixtures, apart from individual compounds, is that the PAHs always appear naturally as mixtures, usually with very similar composition and predictable concentrations relative to the most commonly used indicator of exposure, benz(a)pyrene. Some constituent PAHs have not yet been characterized for carcinogenicity. Combined exposure involving some PAHs which have characteristics of cancer promoting agents, with or without cancer initiation activity, may also produce a positive interaction with PAHs that are direct carcinogens, increasing the carcinogenic potency of the mixture.

The PAHs are also important in combination with other exposures characteristic of firefighting. They are products of incomplete combustion and are responsible for carcinogenesis in many settings, including as constituents of cigarette smoke. They are known constituents of fine and ultrafine particulate matter and of diesel exhaust. An analogous series of chemical compounds are heterocyclic with nitrogen and are also known to be carcinogenic, but these have not been as well characterized. PAHs are the leading exposures imputed in causing the many cancers that are elevated in firefighting.

PAHs have also been associated with accelerated atherosclerosis. Polycyclic aromatic hydrocarbons have been implicated in experimental studies to promote vascular disease and the development of coronary artery disease in animal studies.

The PAHs are also known constituents of fine and ultrafine particulate matter, described above, but their primary role as significant toxic agents for human beings is as carcinogens and in inducing chronic disease. This is a large family of organic compounds, several of which are

known carcinogens. They are products of incomplete combustion and are responsible for carcinogenesis in many settings, including as constituents of cigarette smoke. An analogous series of chemical compounds are heterocyclic with nitrogen and are also known to be carcinogenic, but these have not been as well characterized.

Polyhalogenated Organic Compounds

Polyhalogenated organic substances are organic compounds substituted with chlorine, bromine, or fluorine, which may be formed or released during a fire. Public concern currently revolves around brominated compounds. However, the polyhalogenated hydrocarbons, particularly the dioxins and furans and the polychlorinated biphenyls (PCBs) are more widespread and have been of concern for much longer.

Brominated compounds have been used extensively in the past as fire retardants. Polybrominated fire retardants are heavily used in consumer products to reduce flammability, although their effectiveness is controversial. Although some of the polybrominated biphenyl compounds may be quite toxic, exposure to brominated compounds has not been considered to be an appreciable risk associated with firefighting. This may reflect lack of investigation, since these compounds are difficult to study and work with.

Dioxins and furans (more accurately, polychlorinated dibenzodioxins and –furans, but colloquially called “dioxins”) are potent organochlorine compounds that are formed most efficiently during combustion in the presence of a carbon source at temperatures between 200° and 400°. Unfortunately, this is an optimum window for the formation of these compounds. Below this temperature window, they do not form efficiently and above the window they break up. Dioxins and furans also bioaccumulate because they are metabolized slowly and stored efficiently in lipids. Most of the concern for dioxins and furans comes from their high potency (they are among the most potent toxic agents known) which can cause health effects at very low exposure levels. The primary health effect of concern is carcinogenicity. Whether dioxins and furans initiate cancer has been sharply debated but the consensus that appears to be emerging is that it can and there is no doubt that these compounds are among the most powerful cancer promoting agents known. They have an equally potent effect in inducing metabolism of other so-called “incomplete” carcinogens, enhancing their initiation of cancer by stimulating expression

of enzymes that convert them to a more active form. Thus, for adult exposures, cancer risk drives control and standards setting, even though the cardiovascular system is also emerging as another important target organ. Presumably due to induction of liver cholesterol-forming activity and local effects on the blood vessels favoring atherosclerosis, dioxins are now known to induce and accelerate atherosclerosis and therefore the risk of coronary artery disease in animal studies. In human studies, exposure to dioxins has been associated consistently with increased mortality from cardiovascular disease and especially ischemic heart disease (mostly myocardial infarction, the familiar "heart attack"), although there are many limitations and potential confounding factors in these studies.[50] Whether this is an important effect in human beings is not clear but the potential exists for dioxins to increase the risk of coronary artery disease among firefighters. Dioxins and PCBs also interfere with some hormones, including thyroid hormone, but this is more of a threat to children and theoretically to the fetus than to adult firefighters. Because dioxins and furans are formed *de novo* from combustion products, they are a permanent feature of fire smoke and an continuing management problem.

Polychlorinated biphenyl compounds (PCBs, of which there are 209 congeners) are not formed in settings of combustion but may be released, particularly in fires involving sources, most often electrical transmission and old transformers. Some of the PCB congeners act much like the dioxin congeners described above. Many of the PCBs have dioxin-like properties but generally at much lower potency. The major issue with the PCBs is that most of them are very slow to be metabolized, either by human beings or in the ecosystem, and stored efficiently in lipids. At ambient temperature they persist and are bioconcentrated, with amplification up the food chain. Thus, the more stable PCBs have become difficult management problems in ecotoxicology, very slow to degrade and persisting for years or decades. Many of the congeners (210 each) are toxicologically irrelevant. A few are highly toxic and have effects on the immune system and interfere with hormone activity, particulary thyroid hormone, which has best been described for children in other contexts of exposure. Of greatest concern for adult firefighters, the PCBs are also promoters, if not initiators, of cancer at multiple sites. Most concern for the PCBs and efforts to set protetive standards have therefore centered on the potential for carcinogenicity. Because the PCBs are no longer being produced commercially (with very few exceptions), this problem should be diminishing.

Perfluoroalkyl acids (PFAAs), of which the most commonly encountered are perfluoroctane (PFOA, also called C8), perfluoroctane solfanate (PFOS, the active ingredient in Scotchguard®), and perfluorohexane sulfonate (PFHxS, a carpet treatment), are used as fire suppression chemicals and surfactants. They are found in fire extinguishing foam and surfactant (stain-resisting) surface coatings, Experimental studies have shown possible carcinogenic effects (on bladder) and heart disease. Firefighters have been shown to have elevated levels of PFOS and, significantly, PFHxA but not PFOA in serum; the levels were low and the differences were not great in absolute terms compared to other employment categories, but the coefficient of variation for the greatest difference was 33% (for a mean of 39.28 ng/ml for PFOA). This suggests that firefighters may be at elevated risk of effects from exposure to the PFAAs, depending on the potency and nature of the health effects, if established in human populations.[51]

Trichloroethylene

Trichloroethylene (properly trichloroethene; TCE or "trike"; not to be confused with trichloroethane, which is also called chloroethene) is a solvent used primarily as a degreasing agent. It is very effective, has relatively low flammability for its class, and a relatively high threshold for acute toxic effects, which made it popular first as an anesthetic agent and later as a substitute for much more acutely hazardous organic solvents. It fell out of favor, however, partly because it is chemically unstable in heat but primarily because it became a widespread hazardous waste and contaminant of groundwater. It has since been replaced by other solvents, unfortunately including 2-bromopropane, which has become extremely controversial recently because of its own serious toxicity.

Trichloroethylene is generated in fire smoke because of the presence of abundant chlorine sources but relatively little is generated in cigarette smoke.

In a major new development, trichlroethylene has been recognized as a suspected carcinogen for many years. IARC has classified it as Group 2A (probably carcinogenic to humans based on evidence for humans), the evidence for which is forthcoming in Monograph 106, due shortly. The US National Cancer Institute now considers trichloroethylene as an established human carcinogen. The evidence suggests multiple target organs, including liver, kidney, and, especially, lymphatic system as lymphomas.[16,52-59]

Exposures of Primarily Military Significance

In addition to the exposures discussed above, Royal Australian Air Force firefighters would have been exposed to a variety of toxic agents associated with military aviation and to emissions from the fire pits found at the site.

Fire Pits

Fire pits are trenches in which combustible trash, chemical waste, and invariably some noncombustible materials are doused with (usually) diesel fuel and set on fire. The purpose of fire pits is to dispose of all manner of trash, leading to diverse and variable composition in the emissions. The emissions that result consist of diesel fuel combustion products, products of combustion of the trash stream, and possibly entrained particles of dirt and other material of crustal origin. Emissions from fire pits tend to be highly variable and are determined primarily by burn temperature and composition of the materials.[60]

Burn temperatures are variable but because of the use of accelerants (diesel fuel) probably burn hotter than simple trash fires but not as hot as diesel engines or furnaces. Combustion of diesel fuel in the burn pit does not occur under pressure, as it would in a diesel engine, or which maximum oxygen delivery, as in an incinerator. As a result, the emissions profile would be less rich in fine particulate matter compared to coarse particulate matter. That means that the efficiency of a burn pit is much less than an engineered incinerator. Burns under conditions of inadequate oxygen lead to production of carbon monoxide. Burns at lower temperature, on the order of 400°, generate more complex hydrocarbon species, and coarser particulate matter than a well-designed incinerator. Another implication of burn temperature is that toxic emissions are most likely to occur when the fire is beginning from a cold start and when it is cooling down.

Composition of the material could include plastic materials (including polyvinyl chloride, which becomes a chlorine source for polychlorinated dioxins and furans), electronic components and other materials containing metals, and waste chemicals such as solvents and paints.

Dispersion of the plume from the burning fire pit is likely to be variable but will often result in fumigation, the technical term for a smoke plume that meets or travels along the ground, exposing receptors at ground level. Fire pits are constructed below ground level. Because fire pits do not burn very hot, compared to incinerators, thermal updrafts are less in volume and velocity than emanations from stacks, so the smoke would not usually rise very high. (It would reach a higher altitude in still, cold air). As a result, the dispersion plume from a fire pit is likely to spread horizontally as well as vertically and to fumigate areas downwind, especially in the early morning where a low inversion would be expected.

Jet Fuels

Aviation turbine fuels are based on kerosene. High-performance aircraft require consistent fuel characteristics, which are achieved by blending well-characterized kerosene with other hydrocarbons (desulfurized alkane and aromatic fractions) and adding small quantities of additives for corrosion inhibition, icing inhibition, engine maintenance, bacterial growth inhibition, flow enhancement, and performance. From 1951 to 1990, the basic blended fuel used by most air forces, including Australia, was JP-4 (JP stands for "jet propulsion").

However, there were problems with JP-4. One was that it tended to be irritating to skin, which presented an occupational hazard to mechanics and fuel technicians. Another was that although it was not highly volatile and was difficult to ignite (except in a jet engine), it was still flammable under ambient or shop conditions and so presented a safety risk.

JP-5 was another formulation, with a much higher flash point, previously used to fuel jets on aircraft carriers. For operational reasons and flexibility, air forces have moved to a single fuel platform for all uses and JP-5 has been mostly phased out.

JP-8 was developed as the replacement for JP-4. It has a lower ignition temperature, greater viscosity, and lower volatility, and is also difficult to ignite and is less flammable than JP-4. It is reported be less irritating to skin but slightly more irritating to airways.

Animal testing results to date does not suggest a cancer risk to humans associated with these jet fuels, but this requires interpretation. Like other light hydrocarbons, including gasoline, these jet fuels induce a change in the kidney ("light hydrocarbon hyaline nephropathy") that is associated with expression of a particular protein (α2u –globulin) in the glomerulus that is only

expressed in the male rat, and not in human beings. This condition is associated with initiation of renal tumors, but only in male rats, and has no predictive implications for humans or other species (of, for that matter, female rats if their safety were to be a concern). Thus, cancer bioassays are considered negative for human risk although they may be positive in yield of tumors that arise from this specific mechanism. Large-scale human studies have not been done on workers handling the fuels.

Reproductive risks have not been suggested in toxicity tests except for one positive result in sister chromatic exchange for JP-8. Toxicity evaluation studies for immune or neurobehavioural effects are not available. (Mattie 2011)

All jet fuels have the basic toxicity characteristics of kerosene, which can result in non-specific central nervous system depression with heavy inhalation of fumes or the unlikely occurrence of ingestion. However, kerosene is not a particularly potent toxic agent, even by ingestion.

CARDIOVASCULAR DISEASE

There is a large literature on cardiovascular risk among firefighters. In the interests of keeping this review manageable, accessible to readers, and responsive to the mission of the sponsor to identify compensable conditions, the following section is confined to evidence of chronic cardiovascular outcomes or acute outcomes with disabling sequelae. Papers describing risk factors, cardiovascular health, basic cardiovascular mechanisms using firefighters as subjects, and treatment are outside the scope of this review.

There has long been interest in the issue of cardiovascular disease risk among firefighters and an assumption that the risk is elevated. Empirical evidence for this assumption came in part from studies that showed seemingly high rates of cardiac findings (abnormal EKG stress tests) despite favorable cardiovascular risk factors, which at least in 1975 in Los Angeles, were generally better than sedentary male insurance executives in blood pressure and cholesterol, but not smoking (32% compared to 26%). This led the authors to speculate that there must be an occupational risk superimposed on the relatively low background risk among firefighters.[61]

By 2006, the picture became much clearer. Among firefighters, 77% of retirements of firefighters in Massachusetts were due to coronary artery disease and 23% for other cardiovascular conditions, suggesting an increased morbidity. Only 42% of retirement applications were associated with discrete on-duty events. Of those, fire suppression (OR 51; 12 – 223) and response to alarms (6.4; 2.5 – 17) were associated with extremely high risks, demonstrating that occupational factors contribute greatly to individual risk. At the same time, firefighters who retired due to cardiovascular disease showed a significantly greater prevalence of cardiovascular risk factors than control firefighters. [62] Subsequent studies have replicated and extended this observation, as will be shown. [63]

It is now clear that population risk is predicted by the same risk factors as in the general population, while individual and occupational risk is modified by occupational factors of firefighting.[62] This has provided a new and more comprehensive model for cardiovascular risk among firefighters.[64-66]

Background

Cardiovascular disease embraces a broad spectrum of disorders of the heart and blood vessels, and is intimately connected with diabetes. The major disease mechanisms underlying cardiovascular disease in the general population are atherosclerosis, a complex process that involves changes in the wall of blood vessels due to accumulation of fatty deposits – only some of which are derived from dietary fats – and degeneration of the elasticity of the blood vessel, and hypertension, elevated blood pressure. Among firefighters, these shared risk factors are accompanied by risk factors specific to the occupation, including exposure to cardiotoxic chemicals (principally but not exclusively carbon monoxide), heat stress, physical exertion, and factors of work organization (normal work punctuated by episodic hyperactivity). Cardiovascular disease is manifested primarily by stroke, kidney disease (from hypertension and diabetes), peripheral vascular disease (particularly common in diabetes), aortic aneurysm, and, of course, heart attacks, of which there are two major types, which will be given non-standard but useful working names here. "Ischemic heart attacks" (ischemia means insufficient blood and therefore oxygen supply to a tissue) occur when there is either an obstruction to blood flow to the heart muscle (myocardium) due to occlusion (precipitated or accompanied by "thrombosis", which is blood clotting) or spasm (which can be induced by carbon monoxide) of a coronary artery, or deprivation of oxygen from the blood (which can occur with carbon monoxide or cyanide toxicity). "Arrhythmic heart attacks" occur when there is a disturbance in the electrical conduction system that keeps the heart pumping in a coordinated way, such that it loses efficiency or fails to pump blood effectively, and these can be precipitated by the same risk factors and by a variety of chemicals.

Cardiovascular disease accounts for about 40% of all deaths in North America, primarily in middle age and the elderly, but incidence is rapidly declining, presumably from improved dietary choices, despite the epidemic of obesity and diabetes. Stroke is declining even more rapidly than heart disease, in North America. Against this background, mortality studies of firefighters have generally shown unremarkable results for lifetime mortality, except for an elevation in aortic aneurysm[5 13,67].

Empirical Evidence

At least one recent review from an authoritative source concluded, prematurely, that there was no consistent association in the literature between firefighting and disease outcomes other than cancer.[68] Unfortunately, this is demonstrably incorrect. It is now clear that the overall favorable mortality profile was concealing important anomalies.

It is now becoming clear that what appears to be a benign risk profile in the literature is actually concealing elevated risk in certain circumstances. The current hypothesis, consistent with the evidence, is that most heart attacks among firefighters are due to risk factors shared with peers, and that some heart attacks among firefighters are time- and place-specific and represent the precipitation of events in men (almost always) with preexisting, underlying disease. If this interpretation is correct, then the event that occurs on the job would fall into one of two types: cardiac events that would not have occurred otherwise, and cardiac events that occurred early but that would probably have eventually occurred later, by weeks, months, or years.

Among firefighters, 45% of on-duty deaths are associated with coronary artery disease. These deaths are associated with strikingly high associations with occupational risk factors: knockdown (OR 64.1; 7.4 – 556), training (7.6; 1.8 – 31.3), and response to alarms (5.6; 1.1 – 28.8). Within the field of occupational epidemiology, these risk factors can be fairly described as astronomical. At the same time, the firefighters who succumbed had a significantly higher prevalence of cardiovascular risk factors predisposing to acute events, including older age (≥ 45), current smoking, hypertension, and prior diagnosis of occlusive coronary artery disease.[69] These findings have been repeated in several subsequent studies and show strong consistency.

The latter contingency, of premature mortality in a susceptible group, is called "harvesting" in the epidemiology literature. However, the implications of harvesting are often misunderstood, because the original concept and term were developed to explain mortality trends in the infirm elderly, not robust firefighters.

However, in younger and more robust populations, harvesting is not simply a matter of an inevitable event occurring somewhat earlier than otherwise expected. For younger working people, these risks are not expected in the near future, as they would be for the elderly and infirm. The additional time to a cardiac event might be years in the case of a younger person who experiences premature mortality, not just months. An event may then lead to the loss, both

statistically and in very real terms, of many years of active, productive and disability-free life, with implications for family security. (The formal accounting for this in epidemiology is calculated as "disability-adjusted of life years" which are lost, called "DALYs", which unfortunately are almost never calculated for occupational disorders.) This is because individual susceptibility to a heart attack clearly varies from day to day (for example, by coagulation status) and if a heart attack did not occur on a particular day, the coincidence of circumstances that favor a heart attack might not occur again soon, possibly for a long time. In other words, if a firefighter with heart disease does not die of a heart attack on a given day in a given situation, he (usually) might live many more years. He might even die of another cause before the heart attack which eventually is likely to occur would in fact occur if he lived that long, which would explain why overall lifetime mortality may not give a clear indication of occupational risk.

Longer-term risk, in which a premature cardiovascular event may be made more likely far in the future, for example in accelerating the process of atherosclerosis, may be concealed in mortality figures by competing causes of mortality that act before the subject reaches the most vulnerable period. That firefighters have a form of accelerated atherosclerotic disease has been mooted (including in a series of now-discredited studies of carbon monoxide from the 1970's that will not be cited here). Contemporary evidence for this comes from the observation that asymptomatic firefighters have an increased frequency of abnormal stress test findings, more frequent and more advanced coronary calcium deposits, and deposits in more critical locations on computed tomography compared to asymptomatic patients referred for evaluation of EKG abnormalities.[70,71]

Mortality from Cardiovascular Disease

Against the high background of mortality from cardiovascular disease,[72] the leading cause of death in North America, it has been difficult to demonstrate general causation for mortality from heart disease among firefighters, especially on the basis of underlying disease.

Some population studies have demonstrated an overall elevation in mortality and incidence from cardiovascular disease, although most have not. Ischemic heart disease was found to be elevated among firefighters but more among police, in Connecticut in the 1960's and 1980's, however the excess was described as small [73]; in retrospect, lifetime risk obscured time-

specific risk, as subsequent studies demonstrated. Baris et al., from 2001[11] (described more fully in the next major section, which also explains risk estimates) found a statistically and epidemiologically significant elevation in ischemic heart disease among Philadelphia firefighters (RR 1.32; 1.19-1.45), which drove a significantly elevated risk for all cardiovascular disease (RR 1.12), in the face of a reduced risk for stroke (RR 0.78; 0.62-1.00). Ma (2005) found a marked excess risk for female firefighters (SMR 3.85; 1.66 – 7.58, based on eight deaths) but did not emphasize the finding.[74,75] Feuer 1986 also showed an elevation for heart disease, (PMR 1.2), but the study design used in that study (proportionate mortality analysis) is prone to bias for major causes of mortality, and so the finding was not emphasized at the time.[76] Other studies of firefighters have shown unremarkable risks for heart disease but most have also shown a relatively low risk for stroke.

Historically, however, studies of heart disease among firefighters have been inconsistent[73,77-79] and some have shown excess cardiovascular mortality confined to certain subgroups, such as firefighters aged 45 to 49[80]. Much of the uncertainty has been resolved in recent years by a series of studies conducted by Kales, Softiades, Christiani and other investigators at Harvard. There is now strong evidence that work-related activities may precipitate myocardial infarction in firefighters with pre-existing coronary artery disease.[81,82] There are also several indicators that mortality may take special forms and may have unique associations arising from work as a firefighter.

Many authors have enumerated the reasons why on-duty mortality from heart disease would be expected to be disproportionate among firefighters: [3,41,66,69,83-86]

- Exposure to cardiotoxic substances, including agents that are known to precipitate cardiac events such as carbon monoxide, cyanide, and fine particulate matter and exposures of unknown significance that may accelerate vascular disease (such as perfluorooctanoic acid)
- Exertion, suddenly and without warm-up, especially during rescue
- Exertion- and stress-related sudden acceleration of heart rate, in response to alarms, noise, and physical demands
- Heat stress, which has complicated adverse effects on the heart and blood vessels, and which induces coagulability and release of markers of inflammation
- Dehydration

- Shift work, which is a known risk factor for mortality from heart disease
- Alarm reaction, a neurological reaction apart from psychogenic stress that accompanies the alarm and involves the reticular activation system of the brainstem (sudden alertness), autonomic nervous system response (sympathetic discharge, including accelerated heart rate and increase in blood pressure), and adrenalin response ("flight or fight reflex")
- Psychogenic stress, which is greatest during rescue (firefighters have been known to develop clinical depression after failed rescue attempts)

Heart disease is responsible for approximately 45% of on-duty deaths among firefighters in the United States, but about the same as deaths in the general population from heart disease in the age group 25 (taking into account that firefighters rarely join the fire service immediately after school) to age 64 (beyond the usual retirement age of firefighters), which is 43.5%.[69,84] This is much higher than other emergency response personnel, such as police (22%). At the same time, their on-duty mortality rate is higher than police and no better than the general population, which is unexpected in an occupation that requires high standards of fitness. (Emergency medical services technicians, at 11%, are not a valid comparison because this group tends to migrate out of the occupation at a relatively young age and often overlaps with firefighters.)

Paradoxically, in North America the occupation of firefighting does not show a strong healthy-worker effect[33,79] despite assumptions to the contrary[77,84]. This observation has been taken as evidence for an underlying cardiovascular disease risk, since overall mortality is proportionately driven by deaths from heart disease. Volunteers do have a much higher proportionate mortality from "heart attack" than career firefighters (50%, 39% respectively), suggesting a fitness or training effect.[87] However, most studies of American firefighters demonstrate an overall mortality risk for cardiovascular or ischemic heart disease close to that of the general population.[5,78,88] (Beaumont[18] is a rare exception.) In international comparisons, French firefighters show a robust healthy worker effect, with only about half as many deaths on an age-adjusted basis (RR 0.52; 0.35-0.75) compared to the general male population of France.[89] Likewise, Swedish urban firefighters showed the expected healthy worker effect (RR 82; 72-91).[90]

Triggers of Cardiovascular Events

As triggers for events, activities related to firefighting appear to have as strong an association as underlying risk factors for cardiovascular disease. Firefighters who died of heart disease were older and demonstrated a higher frequency and severity of risk factors for cardiovascular disease, including cigarette smoking, serum lipids, and hypertension, and were more likely to have physician-diagnosed heart disease.[69] These same risk factors, together with diabetes and serum cholesterol level, also predicted that an event would be fatal rather than recoverable but did not predict that an even would take place on or before the age of 45.[91] Activities at the time of the event, however, were highly significantly and as or more strongly associated with demanding work activity compared to non-emergency duties, including fire suppression (odds ratio 64), responding to alarms (5.6), and training (7.6).[81] This strongly suggests that in most cases firefighting activities are acting on a substrate, or underlying condition, of existing coronary artery disease.

The usual circadian rhythm for myocardial infarction peaks in the morning between 8:00 and 9:00 am until 11:00 am with a second, smaller mode in the evening, around 7:00 pm.[92] However, mortality for heart disease among firefighters peaks from noon until midnight and corresponds closely to the frequency of emergency calls.[69] Likewise, seasonality of deaths from heart disease among firefighters also shows an anomaly, demonstrating two peaks, in January-March and in July-August[93], although without relationship to temperature.

On the other hand, most studies that have examined the issue carefully have not shown a lifetime elevation in mortality among firefighters from cardiovascular disease, even accounting for exposure.[3,12] In retrospect, this may be explained by the observation that the heart attacks that take place on duty are a small fraction of heart attacks throughout the lives of all firefighter and that on-duty heart attacks tend to affect individuals who might have a higher risk for heart attack later, in effect bringing forward an event that might happen later in life.

While firefighters have characteristic risk factors of their own, their risk of cardiovascular disease also reliably parallels that of the general population for conventional risk factors.[94] Interest in this topic has led to firefighters being used as a study population for more basic studies of cardiovascular function and risk, even when the results are not directly related to

firefighting.[95] Studies on firefighters are therefore contributing to global knowledge about cardiovascular disease with lessons for everyone at risk.

Occupation-Specific Risk Factors

This section discusses only exposures and work demands intrinsic to firefighting, especially fire suppression. Lifestyle and nutritional factors associated with firefighting as an occupation can be genuine risk factors by the definition of "arising out of work". They are work-related because they are associated with the organization of work, but are not necessarily intrinsic to the work of fighting fires.

An analysis of the "Supplementary Data System" file of "closed cases", a large database of settled workers' compensation claims current up to 1986, suggests that for "heart attack" firefighters were disproportionately represented among fatalities, as they were for temporary disability from "toxic systemic poisoning", which probably mostly represents smoke inhalation.[96] (Table 4) The SDS file, as with most workers' compensation data, have intrinsic limitations relating to selection bias that constrain their use and interpretation but it is noteworthy that these two categories are elevated for firefighters because the principal toxic exposures of firefighters (carbon monoxide and cyanide) are toxic to the heart.

Occupational risk factors for cardiovascular disease among firefighters can be categorized as follows:

- Toxic effects that predispose to acute cardiovascular events
- Toxic effects that predispose to underlying cardiovascular disease
- Physical factors, ergonomic, and exertional factors associated with fire suppression and control that predispose to cardiovascular disease, primarily acute events
- Stress effects, acute and physiological in nature, associated with catecholamine rush and sympathetic autonomic response
- Lifestyle factors that may relate to non-firefighting activities (exercise, diet, snoking habit)

Inhalation of smoke is known to cause transient effects on the heart, whether or not carbon monoxide is involved, leading to loss of heart function and pumping strength.[97] Within

smoke, there are numerous toxic substances that have an effect on the heart. The most important of these that are now known are carbon monoxide, cyanide, and fine particulate matter. The toxicity profiles outlined here can be confirmed in any current textbook of toxicology.

Table 4. Cardiovascular Deaths in Service and Firefighting Duties at time of Death, after work by Kales et al.[81]

Firefighting Duty	No.	%	Rel. Risks*	Note
Fire Suppression	144	32.1	32.1** (136)	Constitutes <5% of activity time
Return from Alarm	78	17.4	2.5 (10.5)	Transient
Fire-station and routine duties	69	15.4	0.2 (---)	Constitutes > 80% of activity time
Alarm Response	60	13.4	3.3 (14.1)	Transient
Physical training	56	12.5	1.6 (6.6)	Est. < 10% of activity time [105]
EMS and non-fire duties	42	9.4	0.6 (2.6)	Variable, depending on assignment

*For all firefighters in a national database developed by the Federal Emergency Management Agency, deriving expected values by proportion of time spent in duty during total activity time. Expressed as relative risk overall and (relative risk compared to fire-station and routine duties); all relative risks are high significant at $p << 0.001$.

** Value checked. Similarity to percentage in next column to left is a coincidence occurring because the expected proportion of deaths during fire suppression, which is the denominator of the PMR, happened to be 1%. The 95% confidence interval for this extremely large risk is 26.4 to 38.1, which is very narrow.

Some toxic exposures may accelerate the development of chronic cardiovascular disease by damaging blood vessels or causing abnormalities in lipid metabolism. This is not currently thought to be the major mechanism of cardiovascular disease in firefighters but may well contribute and with further investigation the role of these toxic exposures will be clarified.

Specific chemical exposures were described in an earlier section.

Physical factors would seem to be obvious, such as heat and the heat-humid synoptic weather conditions. Firefighter deaths do show a bimodal seasonal variation in winter and late summer. However, winter conditions have been associated with a somewhat higher association with cardiovascular mortality and neither temperature nor wind chill explain this.[93] It may be that

the exertional load of winter conditions, due to operating in snow and ice, is as or more important as ambient temperature and heat loss, but there are no relevant data available. The problem is unlikely to apply in Australia in any event.

Response to alarms provokes an acute stress reaction, long before arrival at the fire scene. Acute stress effects are associated with massive release of catecholamines into the bloodstream, splanchnic vasoconstriction, increased sympathetic tone, and heightened vigilance. This has been known for a long time.[98] Heart rate suddenly accelerates and in some susceptible individuals arrhythmias are more likely. Although it is an integral part of the occupation, the response to alarms is "hard-wired", being an exaggeration of a normal physiological response. For this reason, it is unlikely that firefighters ever get habituated to the alarm, although post-alarm effects may be dampened by conditioning.[99]

The alarm effect is most obvious, and has been well recognized, for its effects on heat rate (and therefore oxygen demand) and rhythm, with catechol-induced risk of arrhythmia. However, recurrent surges of catecholamine may play an unrecognized role, because catecholamines (adrenaline and noradrenaline) are primary cardiotoxic agents, capable of inducing cardiomyopathy in extreme situations (such as phaeochromocytoma). Whether this occurs among firefighters with recurrent alarm responses is not known. It would manifest itself as a disproportionate rate of heart failure, cardiomyopathy, and reduced ejection fraction among older firefighters.

Lifestyle and conventional cardiovascular risk factors are discussed in the next subsection.

Lifestyle-Associated Risk Factors and the Metabolic Syndrome

The literature on cardiovascular risk factors and firefighters is very large and reflects the popularity of firefighters as accessible, cooperative, and appropriate subjects in studies of a general nature as well as risks associated with the occupation because of fire station routine and fitness requirements. This subsection will discuss only a few selected observations regarding conventional cardiovascular risk factors because, as noted in the section introduction, a detailed review is beyond the scope and practicality of this report.

Lifestyle factors and metabolic syndrome affect firefighters as they do other populations. The overall risk of cardiovascular disease and precipitated incidents appears to be largely predicted by conventional cardiovascular risk factors. These risk factors are often given exaggerated weight as a critical root cause of an excess of coronary events among firefighters, often with unsubtle implications of victim-blaming. However, this assumption is not supported by the empirical evidence, nor was it in the early literature.[61,91] The idea of firefighters eating heartily in the fire hall and waiting passively for the alarm while doing little or only sedentary activities was always an unwarranted stereotype and does not explain occupational associations with the frequency of cardiac events.

Blood pressure is, of course, a significant risk factor for cardiovascular disease. In an important observation, it was noted that elevated blood pressure levels that fall within the range of pre- or mild hypertension, at levels at which some physicians may not be motivated to treat aggressively, were still associate with elevated risk in this population.[100] This has resulted in undertreatment, at least in the past.[101]

Cholesterol levels, of course, have undergone re-evaluation and re-interpretation for their significance over the years but as far back as 1975 were not observed to be elevated compared to reference males.[61] Awareness is now much increased but the American population (most studies have been done in the US) has grown more obese and the current population distribution of cholesterol levels would have been interpreted as elevated and high risk a few decades ago. Firefighters are no exception to the national trend but the proportion of firefighters treated for elevations in cholesterol has also increased. Even so, a considerable number of firefighters were found in 2002 to be under-treated for their condition.[102]

CANCER

It is often written that there is insufficient data on firefighters to make a determination with respect to cancer risk. Actually, the data available on firefighters are among the most complete that we have for any occupation for risk of cancer. That is why firefighters have been used as a study population to examine broader issues in methodology and workers' compensation.[7] The problem is that most cancers are "rare" (in the epidemiological sense) and so any one study has low statistical power. In such situations, there will always be some studies that are "negative" and some that are "positive". However, epidemiology is not a game played with a scorecard. One needs to examine the individually studies carefully and to look for overall patterns to make sense of it all. The logic of analysis is detailed earlier in this report.

There are many reviews of the cancer risk of firefighters, each of which becomes somewhat obsolete as new information accumulates with further data. This review literature will not be discussed in detail here, in the interest of emphasizing primary sources. Suffice to say that of two major meta-analyses available, Youakim[4] demonstrated a statistically significant elevation among cohort mortality studies for cancers of kidney and brain and for non-Hodgkin's lymphoma, and an elevation among subgroups for cancers of bladder and colon and for leukemia.

However, there is one review that matters above all else, and that is the meticulous evaluation undertaken by the International Agency for Research on Cancer (IARC), the authoritative UN body for cancer statistics and prevention. In 2007, IARC recognized firefighting as associated with three cancers: testicular, prostate, and non-Hodgkin's lymphoma. Firefighting, as an occupation, was therefore classified in Group 2B, "possibly carcinogenic to humans" on the basis of "limited evidence of carcinogenicity in humans". Their criteria more nearly reflect scientific levels of certainty, rather than weight of evidence.[103]

Occupational Risks for Cancer

Firefighting as an occupation involves exposure to many chemical carcinogens, which can be classified into three basic categories:

- Carcinogenic chemicals arising from combustion, including polycyclic aromatic hydrocarbons (PAHs) and their nitrogen-containing analogues, and benzene
- Carcinogenic chemicals incidental to structural firefighting, including asbestos (predominantly chrysotile in North America, probably crocidolite in Australia) and polycyclic chlorinated biphenyl compounds (PCBs) and their corresponding furans
- Carcinogenic chemicals arising from work as a firefighter, including diesel exhaust.

Specific chemical risks are described at the end of this report. The most important route of exposure is inhalation. However, sufficient absorption across the skin occurs that cancer risk may be enhanced due to changes in the kinetics (excretion and metabolism) of carcinogens.[36]

Recently, a paper appeared by the former director cancer surveillance and the registry of Washington state in which he ventured the opinion, providing no evidence, that increased cancer risk in firefighters may be caused by exposure to strong electromagnetic fields (EMF), a conclusion he drew from inferring that the distribution of cancers is similar to cancers purportedly associated with EMF.[104] This is highly unlikely. The spectrum of cancers he cites as a profile is highly nonspecific and many are actually not commonly implicated in EMF research (bladder) or in most studies of firefighters (thyroid, stomach). The association between EMF exposure and cancer risk is highly controversial and much less well grounded on evidence than that for fire smoke. There are many alternative explanations in chemical exposure such that the need to invoke an unlikely cause such as EMF is not compelling. In short, this is not likely to be an etiologic factor for firefighter-associated cancers. It was published in a journal (*Medical Hypotheses*) that has as its reason for existence the airing of speculation to promote discussion, not presentation of evidence.

The Evidentiary Base for Cancer

The Appendix to this report summarizes the overall findings for most studies of cancer in firefighters that examined multiple outcomes. This table should not be used without qualification and elaboration, because the overall risk estimates can be misleading as well as informative. Studies dating from before 1995 will be discussed in detail in the rest of this report when only there is a particular issue or point to be made, as they have been thoroughly discussed elsewhere.

In 1995, we reviewed the current literature on disease risk among firefighters in order to compare findings and to infer magnitude of risk.[79] The strengths and weaknesses of the older studies are described in that report. Since 1995, there have been many more studies that have contributed to the world literature on firefighters and one relatively obscure Australian reference[105], which was published but in an unusual place, has been rediscovered. They are summarized below. In 2006, Lemasters et al. published a meta-analysis that summarized risk estimates for the world literature for most cancer sites.[5] This meta-analysis is very useful in determining the trend of the literature for site-specific cancer rates overall but by its nature is uninformative about subgroups that could reveal important information useful for an appropriate method in causation analysis. Likewise, Youakim conducted a more recent meta-analysis, limited to a few cancer sites that considered duration of employment.[4] These meta-analyses, but not an earlier and now obsolete meta-analysis by Howe and Burch[6] (from 1990) are referred in this report to where they are relevant. However, emphasis is placed on subgroup analysis where sufficient information is available to support the appropriate method.

Giles et al.[105] examined firefighters employed during the decade 1908 to 1989 by the Metropolitan Fire Brigade of Melbourne in the state of Victoria, Australia, with 95% ascertainment and matched them to the state cancer registry to determine standardized incidence, making it one of the earliest incidence studies. The numbers were relatively small and even the highest SIRs showed wide confidence intervals and failed to achieve statistical significance. This paper was overlooked for many years because it was an Australian contribution published in a limited-distribution Canadian government statistical publication. Despite the obvious effort put into the work by the authors, who were investigators at the Victorian Cancer Registry, there were no further reports from the group and there was no follow up in the world literature.

Burnett et al.[88] conducted a very large proportionate mortality study on firefighters in 27 American states from 1984 through 1990, using data from the National Occupational Mortality Surveillance (NOMS) system. Limitations of these data are partially overcome by the sheer size of the database, which, with 5744 deaths among white male firefighters, is beyond what may be achieved in any one cohort study. This system is an example of population surveillance for occupational disease which we have long advocated.[33]

Deschamp et al. [89] studied the recent experience of relatively small number of fire fighters in Paris from 1977, as a prelude to a longer-term cohort study. An elevated SMR was found for

respiratory cancers (1.12), gastrointestinal cancers (1.14) and genitourinary cancers (3.29) among other findings. However, the study is anomalous in several ways, uniquely demonstrating an elevated mortality from stroke (1.19) and a very low overall mortality (0.52), the lowest reported to date among firefighters. Further experience with this cohort and a much more detailed breakout of cancer by site is required to interpret the findings.

Ma et al.[106] conducted a large study using the same database to explore race-specific disparities in cancer mortality. The study was not intended to replicate or overlap with the Burnett et al., as its purpose was different, but it is much smaller and covers a heavily overlapping population, so it should not be considered to be a separate study independent of Burnett et al. For this study, the NOMS database was extended by three years to 1993 but lost data from three states that were removed. As expected, the results were similar. Race as coded on the death certificates yielded 1817 deaths of white firefighters and 66 deaths of black firefighters. Of greater interest is the pattern of race-specific elevations. Ma et al. found an excess of cancer of the brain, specifically, in African-American but not white firefighters. This is an interesting and provocative finding.

Bates et al.[132] reported a study on firefighters in New Zealand from 1977 to 1996, conducted to investigate the observation of a cluster of testicular cancer.[107,108] This elevation was confirmed as finding independent of the cluster. This study is unusual in reporting both cancer incidence and mortality. It reports one of the lowest mortality ratios reported for firefighters (0.58), suggesting a strong healthy worker effect, unlike other studies. Bates et al. observed no significant elevation except for testicular cancer. The authors caution that matching to mortality data and cancer registration data may be incomplete prior to 1990 and suggest that they have greater confidence for findings after this date. Among cancers of interest in this paper, they found a marked increase in testicular cancer and nonsignificant elevations in incidence in the 1977 – 1996 cohort of cancers of interest: lung (1.14; 0.7 – 1.8), which showed a modest increase with duration of service, bladder (1.14; 0.4 – 2.7), brain (1.27; 0.4 – 3.0), and "myeloleukemia" (1.81; 0.5 – 4.6), but not kidney (0.57; 0.1 – 2.1). Limiting the analysis to the 1990 – 1996 subcohort, however, they found the increase in testicular cancer and a deficit in the same cancers, except for brain (1.59; 0.3 – 4.6), and no kidney or "myeloleukemia" cases. A strikingly different picture is observed in the pattern of deaths, however. Mortality among firefighters in the 1977 – 1996 cohort is elevated for bladder cancer (2.73; 0.3 – 9.8) but less than expected for lung (0.86; 0.4 – 1.6), brain (0.68; 0.1 – 2.4) and

"hematopoietic cancer" (0.72; 0.2 – 1.8), and no deaths from testicular cancer. The discrepancy between incidence and morality in cancers with a high case mortality, such as lung, is an anomaly. However, all numbers are small and the authors are candid in describing limitations of the database outside their control.

Baris et al (2001)[11] conducted an exemplary cohort mortality study. This study should be accorded great weight because among recent studies it has exceptional power, spans most of the 20th century, and has the most complete follow-up. The study therefore merits description in detail.

The cohort consisted of 7789 Philadelphia firefighters employed from 1925 to 1986 compared to US white male rates, comprising 204,821 person years of follow-up. The men were hired in their late 20s (on average) and worked for approximately 18 years, with an average of 26 years follow up. Baris et al. examined their cohort by age, duration of employment, job assignment and by number of runs to fight fires (enumeration of responses from the firehall) in three broad ordinal categories.

There were 2220 deaths among the members of the cohort. All causes of death and all cancers were approximately equal to the expected rates for all U.S. white males. The authors did observe statistically significant excesses for colon cancer (RR 1.51; 1.18-1.93). Nonsignificant excesses were reported for cancers of the buccal cavity and pharynx (1.36; 0.97, 2.14); for non-Hodgkin's lymphoma (1.41; 0.91, 2.19); for multiple myeloma (1.68; 0.90-3.11) and for lung cancer (1.13; 0.97-1.32). With >20 years of firefighting, the following cancer sites showed elevated risks: colon cancer (1.68; 1.17-240); kidney cancer (2.20; 1.18-4.08); non-Hodgkin's lymphoma (1.72; 0.90-3.31); multiple myeloma (2.31; 1.04-5.16); and benign neoplasms (2.54; 1.06-6.11).

Baris et al developed a direct index of exposure by assessing risk by three categories of firefighting runs, with low exposure being less than 3322 runs; medium exposure being greater than or equal to 3323 and less than 5099 runs; and high exposure being greater than 5099 runs. Cancer of the pancreas showed a clear dose-response with rose from 1.02 for low to 1.17 for medium to 1.61 for high exposure. Although there were no other tumour sites with exposure-response gradient, when comparing low exposure (1.00) to high exposure, several cancer sites demonstrated increasing risk: stomach, 1.20; pancreas, 1.42; leukemia, 1.22; and benign neoplasms, 2.06. The authors also compared lifetime runs with diesel exposures, including a

category of non-exposed. Although there were no exposure-response gradients, several sites demonstrated increasing risks in the medium and high categories compared to unexposed: buccal cavity and pharynx, prostate, brain, multiple myeloma, and leukemia.

There is also an apparent dose-response for assessment of low, medium and high exposure related to diesel exhaust for mortality from respiratory diseases (but not for any cancer). The risk rises from 1.00 (non-exposed) to 1.37 for low exposure to 1.45 for medium and finally to 1.49 among those in the high exposure group. Interestingly, there is no such exposure-response relationship for number of runs over the career of the firefighter (regardless of diesel exposure).

All of these excesses have relevance to toxicology and inhaled toxic hazards found in the firefighting profession, except the excesses for benign neoplasms. This is a "wastebasket", or residual category of diagnostic rubrics. Thus, it is not clear whether this represents a true elevation in some unusual class of tumour or (more likely) misclassification.

From the Baris et al study, some tentative conclusions emerge from an overview of the epidemiology data. There were no significantly *reduced* SMRs for any of the a priori tumour sites plausibly linked with firefighting: brain, bladder, kidney, and lymphatic malignancies, as one might expect with simply random error. Further, the Baris study adds weight to linkages between firefighting and cancers of lymphatic system and with kidney, and suggests associations with colon, pancreas and prostate cancers.

Ma's second paper[109,110] is a cohort study of firefighters in the state of Florida yielding cancer incidence, not mortality. Studies of incidence will pick up cancers that are rarely or usually not fatal, such as thyroid cancer. The strength of this study is its very large population base and number of person-years of observation (over 413,000) and the accumulation of a very large number of female firefighters (2,017), previously virtually unstudied. However women only entered the fire service in large numbers very recently and so there were only 52 deaths among the female firefighters in the cohort, which makes this still a small incidence study for this subpopulation. The risk of all cancers was significantly elevated for women (SIR expressed as a RR = 1.63; 1.22 – 2.09) but the pattern of cancers that showed an elevated risk among female firefighters suggested bias or confounding in this subgroup: cervical, thyroid, and Hodgkin's disease. There were nonsignificant elevated risks among the women for kidney, stomach, colon and rectum, but not breast. Among male firefighters, the study confirmed

elevated rates of cancers of bladder (1.29; 1.01 – 1.62) and testicular tissue (1.60; 1.20 – 2.09), and yielded an unanticipated finding, thyroid (3.97; 1.45 – 8.65). There was no elevation and actually a lower estimate of risk among men for brain, lung, and cancer of the lymphatic and hematopoietic systems, aggregated.

Bates[111], who also conducted the aforementioned study in New Zealand, conducted a registry-based case-control study of cancer among firefighters in California, comparing the odds of association with cancer types compared to all other registered cancer cases. (Bates 2007) The advantage of this study was the enormous subject population: This work is remarkable in confirming previous patterns of cancer risk (brain, testes, prostate), and in identifying elevations for esophagus and melanoma.

Kang et al.[112] is a registry-based cancer incidence study of 2125 white male Massachusetts firefighters during the years 1987 through 2003. It is therefore not complete or comprehensive as cohort study and covers a relatively brief time period. Using standardized mortality odds ratios (SMOR), the authors compared firefighters to police and to subjects in the registry for which other occupations had been recorded, a highly artificial synthetic population intended to represent the employed population. For all cancers for which there was an elevation (colon, brain, bladder, kidney, and, unexpectedly, Hodgkin's disease) the SMOR was higher when compared to police than to the general population. If one assumes that the frequency of disease is likely to be higher in the general population, this points to a differential in healthy worker effects, in which the healthy worker effect for firefighters (which in any case is known to be small) is significantly less than that for police, another public safety occupation with similar selection characteristics. Indirectly, this is (weak) evidence for an occupational association for these outcomes, since one might expect the two public safety occupations to be similar.

Ahn et al.[113] is a very large cohort study of Korean emergency response personnel, who perform firefighting and rescue duties. Subjects were active from 1980 to 2007 and were alive in 1995. Cancer was identified through registration in the national cancer registry, after a lag of 16 years. This study design may be expected to miss some cancers that developed earlier than 1996, including those that were fatal before 1995 and incident cancers resulting from earlier exposures in which the subject died before 1995 of any cause. The study is therefore biased toward an underestimate of risk. Even so, several significant elevations were found (colorectal, kidney, bladder, and non-Hodgkin's lymphoma, compared to all Korean men. (A smaller subgroup of

responders who did not perform firefighting had unusual characteristics, showing marked elevations in colorectal cancer and in cancers of bone and cartilage.)

Daniels et al.[47] is the latest (2013) contribution, a massive study of cancer mortality and incidence among male firefighters in three cities conducted by the National Institute for Occupational Health and Safety (NIOSH). It is hereafter normally referred to as the "NIOSH Study", as it is regularly among interested colleagues, even though other studies referred to in this report (including Baris et al.[47] and Burnett[88]) have been conducted or supported by NIOSH. The methodology used in the NIOSH Study was more limited and more descriptive than other recent studies, favoring breadth, large numbers (29,993 firefighters), and evidence for or against replication among the three cities (Chicago, Philadelphia, and San Francisco) rather than drilling down for evidence of exposure-response relationships beyond length of service. The Study covered 1950 to 2009 and average date of entry into the fire service was 1968, which actually covers many older firefighters. Because the NIOSH Study overlapped earlier studies of firefighters in Philadelphia (which had also been conducted by NIOSH) and San Francisco (which had been conducted by one of the authors on the team), the studies in those cities are not truly independent but the city-specific findings cannot be directly compared with their antecedents. Although the main report is almost entirely limited to cancer outcomes, chronic obstructive pulmonary disease was included in the main report, apparently as an epidemiological indicator for smoking-related health effects. Supplemental data published on-line together with the main report provide information on other non-cancer outcomes.

The next contribution to the literature is likely to be a combined Nordic study of over 16,000 male firefighters due for publication in 2014 but available now only in abstract. (Demers 2011) The abstract describes some age categories but does not break down by length of service or assignment. It does, however, describe important findings, such as an elevation in mesothelioma rates and adenocarcinoma of the lung. Aside from brief mention in the sections on those two health outcomes, below, the abstract will not be cited in this report further because complete information is not yet available for analysis. This is because undifferentiated rates for all firefighters are useful and relevant to both outcomes but not so much for other outcomes.

Finally, as is well known to the clients receiving this report, there is a national Australian study of firefighters being conducted by Deborah Glass and Malcolm Sim. Its findings are expected to become available in a few years.

Despite the underlying similarity of most studies in design within their class, individual studies vary considerably in evident bias and execution. Knowing the differences among studies helps interpretation greatly. For example, Beaumont et al.[18], while a fine and competently-executed study, is consistently lower in its risk estimates for disease outcomes compared to other studies of firefighters and so tends to distort attempts to pool data. This is also evident in comparing Beaumont et al. against other studies for colon (but not rectal) cancer. For this particular cause of death, the risk estimate derived from Beaumont et al. is close to 1. If this is an underestimate, in the context of generally lower risks in Beaumont than in other studies, it would have a tendency to dilute the summary risk. Beaumont et al. has a rather high percentage weight (7.8%) among the studies and the lower bound of the confidence interval for the summary estimate (0.99) is very close to 1. Thus, a study that generally seems to "lowball" risks across the board may, by itself, have resulted in the summary risk estimate failing to achieve statistical significance.

Several studies examine a population sample and attempt to determine which occupations are associated with which cancers, usually by matching with death certificates[6] or a disease registry[114]. We have observed that the risk estimates for these studies are usually much below those of occupation-specific studies. An exception to this general trend is Firth 1996[115], which reports a more than ten-fold elevated risk for cancer of the larynx among firefighters in New Zealand, a finding not replicated in any other study. These studies are prone to misclassification bias, although the best of them, such as Firth, examine both usual and current occupation and registry studies are known to be subject to deficiencies in case ascertainment[112].

Studies of the proportion of occupations represented in registries or death certificates for a given disease are frequently useful. For example, Figgs 1995 identified firefighters as not only being overrepresented but to demonstrate a pattern consistent with other occupations involving exposure to solvent chemicals, a suspected cause of lymphomas.[116]

Papers often contain errors and it is instructive to know why. One paper using the proportionate method for occupation has on occasion been used to rebut claims for testicular cancer, Golka et al.[156], contains a significant error. On p. 388, it states that "No relevant studies on occupationally related testicular cancer have been published." This flat statement ignores the important paper of Bates et al.[132] (2001), published three years before Golka et al., in a widely-available journal. The probable reason for this omission is that Golka et al.[117] the authors appear

to have been biased in their search procedures and review process toward retrospective and surveillance studies that are based on monitoring data and that examine associations with many occupations, rather than studies that begin with the occupation and look for associations, through either prospective or retrospective methods. Search terms using occupation as the primary rubric are much more likely to miss findings relevant to specific occupations than searching on specific occupations. The methodology of population monitoring, with all its opportunities for misclassification and missed cases, is also more likely to yield systematically lower risk estimates than a well-constructed prospective study of a single occupation. Lipworth[118] presents a similar problem.

In theory, both registry and death certificate studies are likely to be biased by the potential for misclassification of occupation, since information on work is obtained only once and may differ from the subject's usual occupation. For death certificate studies there is an unproven possibility that misclassification of usual against last occupation could be greater than for other occupation because firefighters often retire into second careers. However, they are also likely to retain their identification as a firefighter as a point of pride throughout their life. For registry studies, there is evidence that stated occupation at the time of data collection corresponds well with usual occupation for firefighters, as for other occupations (κ statistic 74.6; 59.6 – 89.5). (Lockhaupt 2013)

Genitourinary Cancers

Genitourinary cancers represent the conventional situation, in which individual diseases are more or less satisfactorily classified and risk estimates probably do reflect the experience of the group for the individual cancers. The various tissue types (urothelial in bladder and kidney pelvis, clear cell and chromophobe in kidney) are known to be induced by cigarette smoke and so an influence of fire smoke is highly plausible. Perhaps for this reason there seems to have been more widespread acceptance of claims by firefighters in this class than for other outcomes. The data are also reasonably easy to interpret by tumor site.

Bladder cancer

Bladder cancer is a urothelial malignancy, meaning that it arises from the lining of the organ, called the transitional epithelium. There is evidence that this tissue is unusually prone to malignant transformation from a variety of chemicals, some of them now withdrawn from commerce because of the risk, and it is also elevated in the chemical industry, after cancer chemotherapy, with radiation, after exposure to arsenic, among cigarette smokers, and in other occupations in which exposure to PAHs occurs. Even so, it is an uncommon cancer, ranking sixth in incidence among men in North America.

The overall pattern for bladder cancer is that individual studies may not show an excess but the literature as a whole shows evidence for an elevation. The meta-analysis from LeMasters[5] (2006) shows a summary risk estimate of 1.20 (0.97 – 1.46); in the LeMasters' evaluation, this suggestive finding was downgraded due to heterogeneity but internal evidence in the studies was not analyzed for evidence of an exposure-response relationship.

The evaluation of LeMasters was influenced by a number of studies that did not show an elevation overall, but several of these showed evidence for an elevation in subgroups or on replication. Burnett et al.[88] found no elevation for bladder cancer. The PMR was 101 for firefighters dying under the age of 65 and 99 for those dying at or over the age of 65. With 9 and 37 deaths, respectively, this is a large collection of deaths by bladder cancer. Using the same database, Ma et al.[106] reported that a not-quite statistically significant elevation of 1.2 was observed for bladder cancer among white firefighters and an elevation (but based on a single case) for black firefighters. The NIOSH Study[47] demonstrated no elevation for bladder in mortality overall or in any of the cities, but a borderline significant elevation for incidence overall (SIR 1.12; 1.00 – 1.25), a higher elevation for first cancer (1.1.8; 1.05 – 1.33 although the isolated but highly relevant finding of incidence among Caucasian men came close to significance (SIR 1.11; 0.99 - 1.24). However, no relationship to duration of employment was observed in the NIOSH Study.

Improving the exposure assessment and examining subgroups experiencing higher exposure increases the risk estimate in Baris et al.[11], which reported a slightly elevated SMR of 1.25 for bladder cancer, with greatest risk being among those hired before 1935 (RR 1.71; 0.94, 3.08), and among those with greater number of runs during their first 5 years employed (RR

2.59; 0.64 - 9.84). This strongly suggests an exposure-response relationship or the reduced effect of confounding factors and should be considered evidence supporting a presumption on the basis of trend, whether or not individual comparisons achieve statistical significance.

Gaertner et al.[119] conducted a case-referent study of occupational risk factors for bladder cancer in Canada for the Medical and Occupational Disease Policy Branch of the Workplace Safety and Insurance Board of Ontario. Cases (887, a large number) in seven provinces were newly identified from 1994 to 1997 and referents were surveyed in 1996. Firefighters were identified as an occupation with an elevated risk estimate but the elevation was not statistically significant. It should be noted that population-based cancer risk studies are usually ineffective in identifying known elevated risks for individual occupations, unless they are very common and the association is very strong. That this association was identified in a study of this design outweighs the statistical inference test.

Ma et al.[75,110,120] demonstrated a significantly increased risk for bladder cancer among both male and female firefighters in Florida (male: SIR 1.29; 1.01, 1.62; female: 10.00, 0.13 – 55.60, based on a single case). Kang[112], with much smaller numbers, demonstrated a similar but not significantly elevated risk when firefighters were compared to police (SMOR 1.22; 0.89-1.69) and to a referent population (SMOR 0.93; 0.93-1.52). The contribution of the Kang data is to show consistency, in that even studies that do not show significantly elevated risk and that are likely to be underpowered for this outcome consistently demonstrate some elevation.

Ahn et al.[113] demonstrated an overall elevated risk for cancers of the urinary tract among Korean emergency responders, who serve multiple roles but are engaged in active firefighting. This large study based on the national cancer registry, which as noted seems likely to be biased toward an underestimate, demonstrated an elevated standardized incidence ratio for bladder cancer (SIR 1.77; 1.08 – 2.73).

Most population monitoring studies of cancer and occupation tend to underestimate the risk relative to occupation-specific studies, which probably reflects misclassification and incomplete case ascertainment. Thus, it is of interest that one Canadian study[119] of incident cancer shows an elevation in risk for firefighters (SIR 1.51; 0.59 - 3.84) although it failed to achieve statistical significance, as [12]did smoking, exposure to hair dyes, and consumption of fried foods, a novel observation for this cancer site. McGregor, reviewing the data for the occupational health institute of Québec (Institut de recherche Robert-Sauvé en santé et en sécurité du travail,

called IRSST) in 2005, concluded that an increased risk of bladder cancer among firefighters is plausible, that the direction of the evidence is consistent, and that individual factors must be taken into consideration. [121] However, given the presence of exposures known to cause bladder cancer and strong evidence of an elevation in the literature that approaches the criterion for a presumption, the preponderance of evidence favors causation and sufficient weight to derive a presumption.

For bladder cancers, latencies are usually measured in decades but under conditions of intense exposure to potent carcinogens tend to be shorter and more variable than for other solid tumours. Aniline dye workers in the 1940's and 1950's showed a latency as short as seven years, presumably due to high, constant exposure which may have compressed the latency period to its absolute minimum. This is not plausible for firefighters. The exposure of firefighters to potential bladder carcinogens is much less than for chemical workers in the 1920's. In Alberta bladder cancer did not appear before age 60 or before 20 years of service and showed a very long peak latency of 40 years. [141]

It would be difficult to accept latency under 10 years for bladder cancer in a firefighter but the literature from other occupations does not rule out latencies under twenty years. One might expect that the duration of service associated with risk among firefighters to be on the order of 15 years. Youakim determined in his meta-analysis that firefighters with more than 40 years of service had the highest observed risk.[4]

Kidney cancer

Cancer of the kidney has become widely accepted as associated with firefighting by conventional criteria.[4]

Cancer of the kidney is predominantly of the form known as renal cell or clear cell carcinoma, which may or may not include sarcomatous elements which confer a worse prognosis. However, 7% of cancers of the kidney are transitional cell "urothelial" carcinomas, which arise from the renal pelvis (the funnel-like collecting system) and are similar to most cancers of the ureter and bladder (collectively often called urothelial cancers).

Other forms of cancer arising in the kidney are rare and are often found embedded in a clear cell carcinoma as part of its variability. The reason this line of argument is important is that

on occasion it has been argued that because the ICD-9 code for kidney cancers (189) is not exclusive for renal cell cancers, a case in which the predominant cell type was urothelial should be treated differently and the epidemiological evidence may be biased by the inclusion of transitional cell. This small proportion is unlikely to bias epidemiological studies significantly, even if there were a difference in risk of urothelial cancers between firefighters and a comparison population. Since urothelial cancers are associated with similar risk factors to renal cell carcinomas with respect to cigarette smoking (and therefore the chemical constituents of cigarette smoke which resemble those of firefighting), one would expect transitional cell carcinomas to have an elevated risk similar to bladder cancer and elevated together with renal cell cancers, although this would be hard to detect in most epidemiological studies. In fact, there would also be an increased risk of urothelial cancers – see bladder, above – but this would also be in the direction of increased risk. In summary, the inclusion of transitional cell cancers of the renal pelvis in the ICD code for kidney cancer is not a serious objection to the evaluation of risk.

Burnett et al.[88] found a marked elevation for cancer of the kidney. The PMR was 141 for firefighters dying under the age of 65 and 144 for those dying at or over the age of 65. With 24 and 53 deaths, respectively, this is a large collection of deaths by kidney cancer. Using the same database, Ma et al.[106,110,120] reported a borderline statistically significant elevation of 1.3 for cancer of the kidney among white firefighters.

An exceptionally strong case-referent study in New Zealand[122] examining occupational associations of renal cell cancer cases demonstrated a highly elevated and highly significant relative risk for firefighters (OR 4.89; 2.47-8.93).

In data from Alberta a marked elevation in mortality risk for kidney cancer was visible in the category 10 – 19 years of employment.[12] Baris and co-workers reported a doubling of risk with an RR 2.20; 1.18, 4.08 among those employed for 20 or more years.[11]

Ma et al. found no elevated risk for kidney cancer among male firefighters in Florida but a high elevation (but based on a single case) among female firefighters (SIR 4.17; 0.05, 23.18).[75,110] Kang, in a more limited sample from Massachusetts, also showed an elevation but much smaller and not statistically, and higher as compared to police (SMOR 1.34; 0.90-2.01) but not to a referent population (SMOR 1.01; 0.74-1.38).[112]

Ahn et al. demonstrated an overall elevated risk for kidney cancers among Korean emergency responders, who serve multiple roles but are engaged in active firefighting.[113] This

large study based on the national cancer registry, which as noted seems likely to be biased toward an underestimate, demonstrated an elevated standardized incidence ratio for kidney cancer (SIR 1.59; 1.00, 2.41).

The NIOSH Study showed a statistically significantly elevated risks for kidney cancer overall (SMR 1.29; 1.05 – 1.58, SIR 1.27; 1.09 – 1.48) and in Chicago (1.62; 1.23 – 2.11) and among Caucasian men (SMR 1.31; 1.05 – 1.60).[47] There is also a suggestive stepwise increase in risk across three decades of employment duration, ending before the last category (30+ years). Taken together, this is strong evidence for an elevation.

It is not clear that latency in kidney cancer follows the same pattern as bladder cancer. Latency has not been as intensively studied for kidney cancer. On the basis of current understanding and the literature on firefighters, it might be difficult to accept an expired time since first exposure of under 15 years, just on the basis of the time required for a solid tumour to proliferate. In his meta-analysis, Youakim found that firefighters with more than 30 years of exposure had the highest risk of mortality.[4]

Certain references on renal cell cancer that have been cited occasionally in the past as refuting an association require clarification. In particular, studies that examine occupation and cancer risk on a population basis using surveillance data usually underestimate the association between the two which is revealed by cohort and case-referent study designs.

Lipworth[118], in an extensive review of occupational associations of renal cell cancer, did not address firefighting. Contrary to its conclusions, which is that occupation in general is not strongly associated with renal cell cancer, other studies published about the same time (including Zhang[123] identified an elevated risk of renal cell cancer for several occupations (firefighters were not studied), and concluded, emphatically, "…occupational exposures may increase the risk of renal cell carcinoma." Moyad[124] was clearer when he wrote "…numerous occupations, occupational exposures, reproductive and hormonal changes or manipulations, and a variety of other factors may impact risk, but *overall* their contribution seems small compared with other more consistent risk factors." [Italics added.] Moyad is saying quite clearly in context that obesity and hypertension are major risk factors driving rates of renal cell carcinoma overall in the American population but that for individuals, other factors are significant, among them occupation.

[redacted]

Given the presence of exposures known to cause kidney cancer and strong evidence of an elevation in the literature that approaches the criterion for a presumption, the preponderance of evidence favors causation and sufficient weight to derive a presumption.

Youakim determined in his meta-analysis that firefighters with more than 40 years of service had the highest observed risk.[4]

Testicular Cancer

IARC already recognizes an association between testicular cancer and occupation as a firefighter.[103] The Lemasters metanalysis found a summary risk estimate of 2.02 (1.30 – 3.13), the highest found in the meta-analysis.[5]

Aronson/L'Abbe (1992) found a high elevation of testicular cancer (SMR 246; CI not reported) but with only three cases.[13] Bates et al.[1]found an odds ratio of 3.0 (1.3 – 5.90) for testicular cancer among firefighters in the New Zealand capital city of Wellington.[108]

Stang et al. reported very similar findings from northern Germany, although their odds ratio of 4.3 (0.7 – 30.5) was not statistically significant.[125] Such high risks are unlikely to be confounded by differences in the prevalence of cryptorchism (the major known risk factor), smoking (not known to be associated with testicular carcinoma) or other plausible alternative risk factors. In their community-based study of testicular carcinoma, only four firefighters and three controls were firefighters out of 269 and 797, respectively, making the power of their study very limited. Stang et al. also reported on duration of employment. Of the four cases, two had been employed as firefighters more than 20 years and two for less than 4.Bates[111] then demonstrated a statistically significant elevation for testicular cancer among California firefighters (OR 1.54; 1.18-2.02).

There are five basic tissue types of testicular cancer, the most common by far being seminoma (about 95%). Bates et al.[132] does not specify the histology of the tumours. Stang et al.[153] reports that of the four in their study, two were embryomas, an unusually high frequency, which suggests, but does not prove, that this type (which is also found in mixed germ cell types) may be uniquely associated with occupational risk.

Given the totality of the evidence, it is reasonable to establish a presumption for testicular carcinoma on the basis of current evidence. However, given the methodological limitations of

Bates et al. [132]and the lack of available evidence on exposure, tissue type of the tumours and latency, no further guidance can be recommended. Testicular cancer was not considered in earlier studies and an excess may have been hidden in aggregate figures for genitourinary cancers.

Notwithstanding these strong associations, the NIOSH Study (Daniels 2013) could show no elevation overall in mortality or indcidence.[47] The numbers of cases were too small to do more detailed analysis.

Prostate Cancer

The question of prostate cancer has come up repeatedly and has been exceptionally difficult. In LeMasters et al., the summary risk estimate was 1.28 (1.15 – 1.43), which was considered a major finding of the study. However, individual studies suggest a much weaker association for this very common cancer, which should be much less affected by power limitations than almost any other cancer.

Prostate cancer, despite a number of studies that appear to suggest an excess, is an example of a diagnosis that does not fit the logical framework required for a presumption. On the face of it, the evidence would seem to suggest a rather weak association with toxicological plausibility. Detailed examination of the problem, however, suggests that this is a spurious association caused by screening bias, which is exceptionally strong in this case. Prostate cancer ultimately does not fit the framework outlined in this report.

Prostate cancer is often found incidental to an examination or evaluation, and common forms of it are not fatal or highly progressive when its onset is late in life. For these reasons, it is heavily under-diagnosed. “Indolent” or “latent” small cancers are often found at autopsy as an incidental finding, especially at advanced ages.

Indolent prostate cancer is a common and virtually inevitable disease of aging men, such that elevations in risk are not really indicative of lifetime incidence. In many, possibly most, cases, prostate cancers have no effect on longevity or symptoms and do not warrant investigation to detect it, in the absence of screening. If screening were not undertaken, the disease would never be detected at all. Autopsies demonstrate a much higher rate of prostate cancers, mostly of the indolent variety, than detection during life. Most aged men do not have autopsies. If they did,

the reported rate of prostate cancer in the general male population would be much higher and more accurate reflect the true prevalence.

Participation in screening programs is now driving reported trends in prostate cancer. The frequency of recognition of prostate cancer in the general population has increased in recent years but mortality from the disease has not. Most observers think that this is because of improved recognition and diagnosis rather than a true increase in incidence. In particular, improved and more intensive and in some cases mandatory screening programs which include tests for detection of prostate cancer may explain all of the increase. When members of a group adhere to (comply with) a screening program for prostate cancer, these previously undetected cancers are identified and counted as cases, although they were there in the population all along unnoticed. Firefighters today participate in intensive wellness and screening programs, often mandatory, and so this so-called "overdetection" of prostate cancer is to be expected.

Comparing a group such as firefighters that adheres closely to screening programs to a reference population that generally does not (such as the general male population) will predictably result in an elevation in reported risk that does not reflect the true incidence of prostate cancer. The group that adheres more closely to screening programs will have many more observed cases of indolent or latent cancer, but probably will experience the same rate (given statistical uncertainty) of the more significant aggressive cancers as the reference population. The result will be an apparent elevation that is driven by detection bias rather than a true difference in rates.

The "prostate-specific antigen" (PSA) test was introduced in 1987 and was rapidly incorporated into medical screening programs for men. Studies conducted prior to the late 1990's may or may not pick up a screening effect. Wellness and screening programs for firefighters were already common at that time and prostate examination was performed using the digital examination method. In general, with the exception of Giles et al.[105] and Demers et al.[126], studies conducted of firefighters before 1990 show no apparent elevation in frequency of prostate cancer. (On the other hand, the elevation seen in Giles is quite high, and occurred in Australia, which had a national health service by 1980, making this study the most significant anomaly in the literature for prostate.[105]) The timing of the increase in prostate cancer reported among firefighters seems to match the widespread introduction of wellness and health promotion programs for firefighters, which place emphasis on screening for the disease.

IARC (IARC Monograph No. 98, 2007)[127] recognizes two studies that show an association between prostate cancer and occupation as a firefighter, Krstev (2008)[128] at a relative risk higher than 3, which is the only study to observe a risk of that high a magnitude, and Bates, with a relative risk about 1.2, which is more consistent with the world literature.[111] Many studies reviewed by IARC showed no elevation. The IARC monograph did not recognize firefighting as an occupation associated with prostate cancer. It only summarized the evidence. Another section of the document, on shiftwork, did imply that a wide range of cancers was associated with changing work shifts, which is characteristic of firefighting, but the connection to firefighting or to prostate cancer was not explicitly recognized. The polycyclic aromatic hydrocarbons have long been recognized by IARC as a group as a Category 1 carcinogen, but not specifically as a chemical risk for prostate cancer.

Demers et al. found that the observed elevation (relative risk 1.4) in prostate cancer demonstrated in his population of Washington state-based urban firefighters (1994) was much reduced when compared to police officers, rather than the general population.[126] Police are a group of municipal employees with similar benefits and comparable physical requirements to firefighters but without the same intense exposure to the characteristic carcinogens associated with firefighting.

Krstev et al. (1998) showed remarkably high elevations for prostate cancer in both white and African-American firefighters (4.75, 2.64, respectively) in a synthetic, combined group of firefighters from Atlanta, Detroit, and New Jersey.[128] The study featured small numbers of cases despite the large population of firefighters, and is the clear outlier because of the high magnitude of the risk estimate.

Ma et al. found elevations in prostate cancer in both white and African-American firefighters but the elevation was small (mortality odds ratio 1.2). [106] The frequency of prostate cancer is elevated in African Americans in the general US population, as is mortality from the disease, a situation which persists.[129] The equalization of relative rates among firefighters implies, but does not prove, that access to healthcare and screening is responsible for at least some of the disparity.

In a large cohort study of workers in the Netherlands who were monitored for prostate cancer, firefighters had a lower rate than the reference population.[130] However, the study was obviously underpowered and because of its unusual design features, bias was difficult to

interpret. Zeegers et al. then conducted a nested case-referent study within the cohort, using as cases the subjects who developed prostate cancer. Because of this study design, they used a 99% confidence interval rather than the usual 95%, making this study was therefore even more under-powered than usual for the detection of infrequent outcomes in individual occupations. However this was obviously not a source of bias because they found moderate reductions, not elevations, in risk among firefighters in their cohort. Other occupations showed substantial elevations. Police showed a very high (4.00) and statistically significant elevation in risk, which was a new finding not replicated in other studies of police.[131] Rubber workers have been known in the past to have elevated rates of prostate cancer in many studies in other studies. In this cohort, they demonstrated a very high RR 4.18 and yet it did not achieve statistical significance. This suggests that although the study was large, the power to detect an excess in any one occupation was low. This study, for all its complications, lends little or no support for an association with prostate cancer.

Bates et al. (2007) demonstrated a statistically significant elevation for prostate cancer among California firefighters (OR 1.22; 1.12-1.33).[111]

A persuasive study that illustrates the complexity of the issue is that by Ahn et al. on Korean fire-rescue personnel.[113] They showed an elevated overall relative risk (1.60) but when divided into personnel with firefighting duties and those without the predominant risk elevation was among the non-firefighters (1.32 and 6.01, respectively) who were mostly administrative personnel working the same shifts, all calculated relative to the general Korean male population. These findings are contrary to what would be expected if firefighting were the operative risk factor but consistent with an employment effect and access to screening services and were observed for many other cancers. It was demonstrated in the paper that Korean fire-rescue personnel in general have much better health status than the general population, which may imply better health care and access to better screening services for a longer period. (Korea instituted mandatory national health insurance in 1977 but it did not cover all of the general population until 1989. Government employees, including fire-rescue personnel, joined the program in 1979.) The findings of this study, on balance, do not support an increased risk of prostate cancer for firefighters despite the appearance of a somewhat elevated risk estimate.

The NIOSH Study found no elevations (risk estimates very close to 1) except among non-Caucasians for both mortality (SMR1.64; 0.95 – 2.63) and significantly for incidence (1.26; 1.02

- 1.54).[47] This is consistent with known racial differences and might also reflect disparity in health care among minorities. There was no association with employment duration.

Evidence for an association between occupational and environmental exposures and prostate cancer has been much searched for but elusive, except for a consistent association with farming. Although an association has been found or suspected in some studies of firefighters, usually with low risk estimates, the totality of evidence does not support a presumption for firefighting. A study of 15 million residents of five Nordic countries, in which the authors concluded "The most common cancer among men in the present cohort was prostate cancer (339,973 cases). Despite the huge number of cases, we were unable to demonstrate any occupation-related risks. The observed small occupational variation could be easily explained by varying PSA test frequency."[132] The absence of an occupational association would include firefighting.

Prostate cancer is virtually a normal disease of aging for men, with a progressive incidence with age so steep that it would be nearly universal if men lived long enough. Although some cases can be devastating, and aggressive prostate cancer has touched many lives, many and probably most prostate cancers do not cause death or even inconvenience during life. This is because most of them are "indolent" or latent", meaning that they grow slowly and are not aggressive.[133,134]

Most men never know that they have prostate cancer and never would without screening, because only a small fraction of prostate cancers behaves aggressively enough to cause symptoms and threaten life. Even many invasive prostate cancers are missed entirely during life although they can be demonstrated at autopsy.[135-137] The rest are "indolent", meaning that they grow slowly and do not invade, and so would not otherwise be detected during a man's lifetime. The result is a "reservoir" (the term used by some investigators) of previously undetected cases that can be found if one looks hard enough.

Screening is known to result in a larger yield of cases of prostate cancer than would be expected from the general population. It identifies mostly indolent cases that would not otherwise cause death or disability.[16, 168-170] The magnitude of this "overdetection" (detection of tumors but without public health benefit) is reported to be approximately 30% or 40%, similar to the reported increase observed among firefighters. The widespread adoption of screening for prostate cancer (especially using prostate-specific antigen, PSA) has been associated with a large

increase in reported prevalence but no change in mortality, demonstrating that these additional cancers are mostly indolent (which is not to say that they are "benign" – they are true cancers but only growing much too slowly to cause problems clinically). The more screening that is performed, the more these indolent cancers are detected and counted in cancer incidence studies but they were there all along.

Australia has a high incidence of prostate cancer detected and historically was aleader in screening for this cancer. The differential, then, between firefighters and the general population may be less because the health care system supports early screening. In Canada, where residents enjoy equitable access to healthcare and there is less difference than in the US between benefit plans for firefighters and access to care by the general population, no excess of prostate cancer was found among firefighters in Northeastern Ontario compared to the general male population among residents older than 50.[138]

Firefighters almost always operate under contracts with negotiated benefits that provide access to good quality health care, comprehensive insurance that supports testing, health facilities that encourage it, and, especially, high participation rates in programs that promote it or may even require it. For example, the Dallas Fire Rescue Department is one of many that have established a wellness program in which regular screening for prostate cancer is conducted.[139] Not surprisingly, more cases are observed in such populations.

The relative risk in the LeMasters study was 1.28, for an attributable risk of 22%, which would be quite consistent with screening bias.[5] None of the individual studies they entered into the meta-analysis showed a risk even approaching that magnitude, interestingly.

Interpreting studies of an occupation that characteristically has excellent health coverage and benefits, such as firefighters, screening bias becomes very important. Prostate cancer screening is widely practiced in the benefits plans for firefighters and has been heavily promoted as part of routine health screening, as in the many programs available to firefighters. Therefore one would expect that a heavily screened population would show an apparent, but not real, excess compared to the general population but not compared to other populations that are routinely and intensively screened for cancer. This is exactly what is observed for firefighters and prostate cancer.

Still, there may be an association between intense exposure and risk of prostate cancer that may apply in individual cases although not necessarily in general causation. Taken together,

the literature on prostate cancer could be construed as suggesting an association but one that falls well below a balance of probabilities. Toxicological investigations and studies of populations intensely exposed to certain agents to which firefighters are exposed (PAHs and diesel exhaust, specifically) do show an elevation in risk of prostate cancer. There may be an association between prostate cancer and exposure to PAHs, and possibly other products of combustion, in individual cases in which exposure is exceptionally high. An exceptionally young age at detection or intensity of exposure may be a marker for an individual case in which occupation may play a role.

For the most part, prostate cancer is not closely or consistently associated with any known carcinogen, not even cigarette smoking. Various individual studies have suggested an association or prostate cancer with exposure to cadmium, cutting oils, diesel fuel and fumes, herbicides, polycyclic aromatic hydrocarbons (PAH), polychlorinated biphenyls, soot, tar, mineral oil, and solvents. The more focused of these studies have yielded inconsistent results with diesel emissions as the most plausible association observed to date, attaining a remarkably high risk estimate of 3.7 in one study from Germany.[140] Firefighters are exposed to diesel emissions, and so it is plausible that there may be a contribution to risk in individual cases (for example, a young firefighter with exceptionally intense exposure), but this is not sufficient evidence to conclude general causation.

If PAHs, which are the predominant combustion-related exposure associated with firefighting, is a major risk factor for prostate cancer as it is for other cancers, one would expect the risk to be closely associated with cigarette smoking, which is the major source of highly intense exposure to PAHs in smoking adults. However, the relationship of prostate cancer with cigarette smoking is weak.[141]

The conclusion to be drawn from these studies is that it is possible to make an individual case but the evidence is not yet sufficient and not yet demonstrated to a balance of probabilities that, in cases of intense exposure to PAHs, the risk of prostate cancer may be elevated among individual firefighters. The risk of incident prostate cancer over a lifetime for men is already so high that it depends much more on longevity than occupation as a firefighter.

Taken as a whole, the evidence suggests that if there is an association and the occupation of firefighting mediated by exposure to combustion products and possibly diesel exhaust, it would have to be demonstrated in the individual case. However, the characteristics of prostate

cancer and the high incidence of the indolent form among aging men do not support a conclusion of general causation.

Brain

Youakim[4] and LeMasters et al.[5] both demonstrated elevations in risk for brain cancer among firefighters using conventional criteria of meta-analysis. In LeMasters et al., the summary risk estimate was 1.32 (1.12 – 1.54), but this was downgraded as a major finding of the study.

Cancers of the brain arising from brain tissue are relatively rare and may include twenty or more individual types. Each type may or may not be a different disease, with its own risk factors. Epidemiological studies do not distinguish among them because they are individually rare, subject to miscoding and are aggregated into a more general ICD code when they are reported. The most common type of "brain" cancer is glioma but this type only constitutes about half of the total. Gliomas (astrocytomas) are much more likely to be associated with environmental and occupational exposures than other types of brain tumour, and appear to be most consistently associated with occupations involving solvent chemicals,[142] which are also present as constituents in fire smoke. The risk of brain cancer as an aggregated category is increased in many studies but this risk is probably diluted by inclusion of cancers (and, in the past, meningioma) that are not associated with environmental or occupational factors. This leads to an inherent bias to underestimate the risk for that subset of cancers that may have a true association with firefighting. Analysis by specific tumour type might identify which, if any, is associated with the risk but these cancers are uncommon and such a study would be very difficult; require large populations and will probably not be done anytime soon.[7]

McGregor noted that there "is a tendency for risk of brain cancer to be higher than expected in firemen across the majority (10) of the 16 publications considered" but stated there are many uncertainties and that biological plausibility was lacking.[143] However, McGregor was basing his conclusion on the standard of scientific certainty, which is not the standard of adjudication. The basis for his conclusion regarding plausibility is not clear, because the astrocyte, the cell of origin of gliomas, is metabolically active, involved in transport, and lipid-rich, characteristics that would seem to favour chemical carcinogenesis.

A different approach is required to determine occupational risk within this category of tumours, inferring risk for the predominant type from the combined risk for the group. One can expect that the magnitude of elevated risk for glioma will be diluted by aggregation with non-glioma brain tumours. Therefore any consistent elevation in the rubric as a whole is likely to be an indicator of elevated risk for gliomas but the magnitude will be attenuated by dilution.

For firefighters in the US Pacific Northwest active in the 1980's, Demers et al. documented a doubling or risk (SMR% 257) at less than ten years of employment peaking at over a tripling (353) up to 19 years.[144] Heyer et al. also showed a near-doubling of risk (184) at less than 15 years duration of exposure in the same populationj.[145] It is not clear what the minimum latency for a brain cancer might be, especially for rapidly-growing astrocytoma. It would be reasonable to assume that for aggressive brain cancers, expired time since first exposure may be under ten years in some cases.

Bates (2007) demonstrated a statistically significant elevation for brain cancer among California firefighters (OR 1.35; 1.06-1.72).[111] Krishnan (2003) examined the association between glioma incidence and occupation in California and found remarkably high odds ratios for firefighters, both as longest-serving occupation (OR 5.88; 0.70-4301) and ever-employed (OR 2.85; 0.77-10.58), but the study design was intrinsically low-powered for any one occupation and neither achieved statistical significance.[146] Kang found a statistically significant elevation in risk among firefighters in Massachusetts compared to police (SMOR 1.90; 1.10-3.26), which remained elevated but lost significance when compared to a referent population (SMOR 1.36; 0.87-2.12).[112] Thus there appears to be consistency in the risk estimates for this aggregated cancer category within positive studies.

Ma et al. reported that no elevation was observed for brain cancer among white firefighters.[106] In her study of Florida firefighters she found a deficit (SIR 0.58) among men and no cases among women firefighters.[110] Burnett did not observe an elevation for cancer of the brain.[88]

Baris et al. observed a relative deficit of brain cancer, with an SMR of 0.61 (0.31-1.22).[11] Risk did not appear to be concentrated in any subset of firefighters by assignment, number of runs, or duration, although the highest SMR (1.18) was observed among firefighters with more than 729 runs in the first five years of duty. Because brain is an uncommon tumour site, statistical power is usually limited, even in large cohort studies. This study therefore does not

invalidate the findings of other studies that suggest an elevation in risk (upper limit of the 95% CI was 1.22), but it does not support them either.

The NIOSH Study (2013) found no elevation, overall or in any subgroup.[47]

Youakim, in his meta-analysis, showed that firefighters with over 30 years of service were most at risk.[57]

The weight of evidence to date, predominantly from earlier studies, suggests that the elevation in risk for brain cancer reflects a true risk, probably for gliomas, which may be concentrated in certain subgroups, as demonstrated for African-America firefighters, the estimates for which are diluted by inclusion into the rubric of tumour types that are not associated with occupation.

Leukemia, Lymphoma, Myeloma

This disease aggregation represents the most difficult interpretive situation because of the medical heterogeneity of the rubric, with only some indications of which individual diseases are driving the elevated risk. Although heavily used in the past, the grouping of these three cancer types has always been recognized by epidemiologists with any clinical experience to be an illogical combination.

"Leukemia, Lymphoma, Myeloma" was once a common aggregation in epidemiological studies. However, it is not a medically defensible aggregation of disease outcomes. The disease categories are distinct, although there is some overlap, and each category consists of individual disease with very different characteristics. Most epidemiological studies aggregate deaths or incident cases in these three broad categories, and even more commonly together, in order to achieve sufficient numbers for statistical analysis. However, the legitimate purpose for doing so must be to make a provisional assessment, to determine if there is an anomaly. When these aggregations are taken at face value, as if they constitute a single disease outcome, elevations in one disease or a deficit in another can easily distort the aggregate risk estimate.

Non-Hodgkin's Lymphomas

IARC already recognizes an association between non-Hodgkin's lymphoma and occupation as a firefighter.[127] Both Youakim[4] and LeMasters et al.[5] recognized a highly significantly elevated risk by conventional scientific criteria in their meta-analyses (in Lemasters, 1.51; 1.31 – 1.73). McGregor, on the other hand, concluded that the evidence was insufficient to come to any recommendation but could not, even using conventional standards of scientific certainty, rule it out.[147]

Lymphomas are uncommon but about twice as common as leukemias. There are many recognized lymphomas, each of which is a distinct disease. Together, they tend to contribute a small number of deaths in most studies and are difficult for epidemiologists to assess as a group, let alone individually. Because there are so many lymphomas, they are individually rare, and many tend to manifest themselves at older ages, their relationships to environmental factors are more difficult to determine even than the leukemias.

Large-scale population-based epidemiological studies in the past generally did not separate out the various types. When they did, they divided non-Hodgkin's lymphoma into the obsolete categories "lymphosarcomas" and "reticulum cell sarcomas", which are only slightly more informative than the aggregated rubric. More recently, they usually divide lymphomas into simply Hodgkin's disease and non-Hodgkin's lymphomas. Hodgkin's disease is actually a class of apparently closely related lymphomas that tend to peak in young adulthood and again at older age and have not been associated with occupational or environmental exposures or occupational risks. (There are two studies that suggest an excess among firefighters, but the literature is not ready for evaluation, in our opinion. Hodgkin's disease is thought to be unlikely to be associated with external exposure.) Non-Hodgkin's lymphomas are a larger, even more heterogeneous category and have long been known to be associated with many environmental exposures and occupations involving chemicals, particularly involving herbicide exposure, dioxins and furans, and, most recently, solvents, especially trichloroethylene.) Chronic lymphocytic leukemia, which is more accurately considered a lymphoma appearing in blood, has been identified as a risk of Vietnam veterans exposed to herbicides on this basis, although leukemias in general, are not so recognized. It has been clear for decades that each lymphoma is a specific disease, with its own risk factors. It is clear, therefore, that combining all lymphomas will not yield a meaningful measure of risk for etiological research, regardless of the statistical advantages of aggregate numbers.

There are over 30 types of lymphoma recognized in the current classification system. New types will certainly be identified in the future as genomic methods become more sophisticated. Different types of lymphoma are known to be associated with different occupational risk factors: follicular cell lymphoma with the meatpacking industry and small cell lymphoma and diffuse large B-cell lymphomas, with solvent exposure.[148] The broad group of large B-cell lymphomas, of which there are at least 13, by itself appears to be a collection of diseases likely to have different causes.[148] The category includes diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and a form of lymphoma that overlaps with chronic lymphocytic leukemia (small cell lymphocytic lymphoma), among other major types, and several even less common diseases, including Burkitt's lymphoma (which is known to be associated with the Epstein-Barr virus), Waldenström's macroglobulinemia. Clearly this is a very heterogeneous category.

However, DLBCL and follicular lymphoma lead the others in incidence. DLBCL is the most common, at approximately 25% of all lymphomas and follicular lymphoma is second, at about 20%. If the risk for DLBCL alone, were to be 2.0, then this by itself would elevate the risk for all lymphomas to 1.17, which is in fact very close to what is observed in many studies. (This does not suggest that DLBCL is in fact doubled – that is not known, although it may well be. This example illustrates that how that would affect the risk estimate for the entire rubric if it were. There may be other lymphomas that are elevated but at present there is better evidence for DLBCL than for others and preliminary evidence for a causal association. (This will be detailed later in this section.)

For this reason, when a study shows an elevation in the category of "non-Hodgkin's lymphoma", it really indicates that some but not all of the 30 diseases that make up that category are elevated, not that risk for every lymphoma across the board is elevated. Likewise, when the elevation is modest or even absent, it does not mean that the risk of a particular lymphoma is *not* elevated for the group. The inevitable conclusion is that summary risk estimates for the lymphomas as a class do not describe the risk for specific diagnoses within the lymphomas for exposed workers, specifically firefighters. In other words, just because the overall risk for non-Hodgkin's lymphomas as a group may be elevated to, say, 1.50, this does not mean that small B-cell, diffuse large B-cell, follicular, Burkitt's, or any of the several T-cell lymphomas are all elevated to the same degree, or even elevated at all. Given an elevation in the class as a whole,

the most parsimonious explanation is that if there is an elevation in one type that is sufficient to elevate risk for the whole group, it is more likely to be in the more frequent type, which would be diffuse large B-cell, rather than a much higher elevation in a less common type, because other types contribute so few cases. However, this is supposition, not fact. It is also possible that there may be elevations in more than one type.

Lymphomas, as a broad generalization, are thought to be caused variously by viruses, chemicals (solvents, pesticides, and chlorinated hydrocarbons have been implicated), persistent antigenic stimulation, or immunosuppression.[149] Not much is known of which exposures in firefighting likely to cause non-Hodgkin's lymphoma, although there is a suggestion that chemicals found at fire scenes that are also identified as solvents, particularly trichloroethylene[16,52-59] or chemicals that track with it in concentration, may be associated with elevation in risk of non-Hodgkin's lymphomas in other settings.[16,53,55]

If, as seems plausible, different environmental exposures are associated with functional changes in different cell types of non-Hodgkin's lymphoma, then the etiology of a particular lymphoma may be more or less specific. A truly elevated risk that arises, for example, from exposure to some constituent of combustion products, may be diluted by inclusion with all the other types of lymphoma, that have no association with the exposure. Analysis by specific tumour type might identify which, if any, is associated with the risk but these cancers are uncommon and such a study is probably not feasible for a single occupation.

Lymphatic cancers were separately addressed in Burnett et al., which revealed an elevation for non-Hodgkin's lymphoma.[88] The PMR was 161 for firefighters dying under the age of 65 and 130 for those dying at or over the age of 65. With 35 and 66 deaths, respectively, this is a large collection of deaths by lymphoma. These cancers were also separately identified by Ma et al.[106] who found a statistically significant elevation of lymphatic cancer was observed among white firefighters, with a MOR of 1.4. Among Florida firefighters, Ma et al. found no elevation among men (SIR 1.09; 0.61-1.80) but a large elevation among women firefighters (SIR 33.30; 0.44-185.00) but based on a single case.[110] (Ma also found an elevation in risk for Hodgkin's disease, SIR 6.25; 1.26–18.30, although this lymphoma is not generally considered a plausibly occupational disease and is rarely elevated in occupational studies.)

Baris et al.[11] observed a not-quite significant overall elevation for non-Hodgkin's lymphoma, with an SMR of 1.41. While not achieving statistical significance, this rose to 1.72

for firefighters with 20 years or more experience and 2.65 for those assigned to ladder companies. The subset hired between 1935 and 1944 did show a statistically significant elevation of SMR 2.19 (1.18-4.07). A reverse dose-response relationship was observed by number of runs, with the group experiencing the lowest number showing a significant elevation, with an SMR of 2.36 (1.31-4.26), but no relationship was found with runs during the first five years. Baris et al. found that among those employed more than 20 years, the SMR was 2.20; 0.90,3.31). This suggests the possibility that these are true elevations in these subgroups.

Ahn et al.[113] demonstrated an overall elevated risk for non-Hodgkin's lymphoma among Korean emergency responders, who serve multiple roles but are engaged in active firefighting. This large study based on the national cancer registry, which as noted seems likely to be biased toward an underestimate, demonstrated an elevated standardized incidence ratio for non-Hodgkin's lymphoma overall (SIR 1.81; 1.12, 2.76).

Kang did not show an elevation (SMOR 1.10; 0.58 – 2.09 against all other occupations, 0.77; 0.31 – 1.92 against police),[112] but its predecessor study (Sama 1990) did, achieving high statistical significance against police (1.59; 89 – 284 and 327; 1.19 – 8.89).[150]

The NIOSH study has demonstrated a non-significant elevation (very close to borderline significance overall and in Philadelphia) of NHL (and an increase in risk for San Francisco compared to the original Beaumont study).[47] Of particular interest is that it showed a strong and significant association between risk and duration of employment, for mortality and an elevation after two decades of employment (only) for incidence,

Among population monitoring studies, Figgs et al.[116] found an extraordinarily high and highly significant risk of non-Hodgkin's lymphoma in firefighters in 24 states (MOR 5.6; 2.5-12.3) and demonstrate a strong parallel in this pattern of elevation to other occupations involving exposure to solvent chemicals.

In that regard it is of interest that the two most common lymphomas, follicular lymphoma has been significantly associated with solvent chemicals, both in general[148,151] and in a specific association between DLBCL and solvent chemicals appear to be associated the chlorinated hydrocarbons such as trichloroethylene (a degreasing agent.[53] Trichloroethylene is known to be present in modern fire smoke, is absent from cigarette smoke, and is a known, IARC-recognized carcinogen. Other chemicals may track with trichloroethylene in the same way that a variety of volatile organic compounds track with benzene. It is also possible that benzene itself is

associated with increased risk of specific lymphomas, although studies of benzene-exposed populations vary widely in reported risk for outcomes for the lymphomas.

Thus, the weight of evidence, although not scientific certainty, appears to favor acceptance of DLBCL as a lymphoma associated with firefighting. Follicular lymphoma is also associated by the weight of evidence.[53] The situation for other lymphomas is not so clear. They are individually even more uncommon diseases and evidence is simply lacking. That does not mean that they are not associated with firefighting, but that direct evidence is lacking.

The latency period for non-Hodgkin's lymphoma appears to be very long in most cases, with latencies as long as 35 years frequently cited. It is possible that the gradual decline in function of the immune system with age allows an existing quiescent or suppressed lymphoma to grow and present itself and that this would explain the peak presentation of these diseases in the eighth decade of life.

The minimum latency can be very short, however, with other causes. For example following HIV infection and the onset of AIDS. Cases of lymphoma following the sudden onset of immune deficiency are relatively obvious, clinically. However, the problem of minimum latency requires interpretation and clarification. The key is latency from what point? It is possible, indeed likely, that in some cases the onset of immune deficiency would allow a lymphoma that is previously quiescent or suppressed to grow and present itself. In that case, the usually long latency would just be truncated. If a lymphoma is caused by the immunodeficient state, however, which seems to be the case with HIV/AIDS, the latency could be very short, perhaps five years or less.

Leukemias

Haematopoietic cancers (which affect the blood-forming organs, most particularly bone marrow) are generally known as leukemias, which are a family of disparate diseases. They are uncommon diseases, about half as frequent as non-Hodgkin's lymphomas. There are about a dozen well-recognized forms of leukemia, of which five or six predominate. One relatively common type, chronic lymphocyctic leukemia, is generally considered to be more properly classified as a lymphoma. Different environmental exposures may be associated with different cell types. Acute myeloid leukemia (AML) is known to be associated with benzene exposure,

irrefutably. AML is the most common leukemia in adults and this leukemia has been the subject of many studies. Individually, leukemias are relatively rare. A truly elevated risk of AML, which may arise from exposure to benzene in combustion gases, may well be diluted by inclusion with all the other types of leukemia, many of which may have no environmental association. Unless studies are conducted on specific leukemias among firefighters, this problem cannot be resolved and the risk within the class must be inferred from the available data. Such research would be difficult because of the need to accumulate sufficient numbers of cases but not as difficult as for the lymphomas, with their greater number of individual diseases.

McGregor, using a standard of scientific certainty, concluded that an association between benzene and acute myelogenous leukemia was biological plausible but that the epidemiological evidence was not supportive for other leukemias.[152] He recognized that a substantial obstacle was the paucity of studies that addressed hematopoietic cancers separately and individually. LeMasters et al., in their meta-analysis, concluded, using their standard of scientific certainty, that leukemia as an outcome (without differentiating among them) was possibly associated with occupation as a firefighter.[5]

Haematopoietic cancers were separately addressed in Feuer et al. (1986) which found a non-significant elevation of PMR 1.86 (confidence interval not reported).[76] Burnett et al. reported a PMR of 171 for firefighters dying under the age of 65 and 119 for those dying at or over the age of 65.[88] With 33 and 61 deaths, respectively, this is a large collection of deaths by leukemia. Ma et al.[106] observed no apparent elevation for haematopoietic cancers, with an MOR of 1.1 among white firefighters. Among Florida firefighters, she observed no elevation in male and no cases in female firefighters.[110] Elevations were also absent in the recent NIOSH study[47] and a recent study from Korea (Ahn)[113], although an odd classification category in the latter ("lymphohematopoietic cancer") raises the possibility of misclassification and there was a rather high risk (1.68; 0.22 – 13.06) when firefighters were compared to non-firefighting members of the same department (emergency medical technicians). .

Baris et al.[11] found no overall elevation for the leukemias (SMR 83; 0.50-1.37), not specified as acute or chronic or by type. A statistically significant elevation in SMR of 275 (1.03-7.33) was observed for firefighters assigned to ladder companies only, but not to those assigned to both ladder and engine companies. A non-significant elevation was observed for those with a high level of runs in the first five years, with an SMR of 2.44 (0.70-8.54) and with medium (but

not high) levels of runs over a lifetime, with SMR of 2.50 (0.56-11.10). These data are not compelling evidence for a true association in this population but do not rule it out. Because of power considerations, the study by Baris et al. does not really clarify this issue.

There is also an important anomaly in the older literature. Aronson/L'Abbé and Tomlinson, in a study of firefighters in Toronto, uniquely reported risk for types of leukemia. [13] They observed an excess of "lymphatic" [lymphocytic] leukemia at 190 (42 – 485). This finding was highly influential in the IDSP report[67], but is anomalous. Acute myeloid leukemia (AML) would be expected to be elevated in circumstances in which benzene is a hazard, not lymphocytic. These findings suggest that it is premature to limit the presumption to AML.

Although Ontario now recognizes lymphocyctic leukemia, the evidence presented by Aronson/L'Abbé and Tomlinson cannot be used to rule out the possibility of an association with AML. The evidence suggests (again, at the level of "more likely than not") that it cannot, be convincingly argued that only one form of acute leukemia, either myeloid or lymphocytic, should be recognized. Lymphocytic leukemia is suggested by the empirical data, AML by the known toxicological profile of exposures experienced by firefighters. Thus, it is not possible to recommend a selective criterion that only recognizes AML, lymphocytic or, for that matter, only acute and not chronic leukemias.

Thus, at least for acute myelogenous leukemia, a presumption is well grounded. However, the evidence is not clear enough to exclude other types and all types of leukemia combined. Giving the benefit of the doubt to the claimant, as required, suggests that a rebuttable presumption for leukemias as a class is the most defensible policy on the evidence.

Leukemias tend to have short latencies, on the order of five years or so. Short latencies and therefore duration of employment for leukemia are reasonable, on the order of four years to ensure that no errors of exclusion are likely.

Myelomas

Myelomas are B-cell lymphomas and malignant plasma cell dyscrasias, classified differently from the lymphomas for historical reasons, because the abnormal proteins they express have certain characteristics, and because of their clinical manifestations as cancers. McGregor concluded that there was no evidence supportive of an association, based on the

standard of scientific certainty.[153] LeMasters et al. demonstrated a reported a relatively high overall elevation in the literature up to that time (summary risk estimate 1.53; 1.21 – 1.94), making it a major finding of her study.[5] This is where matters stood until about 2008.

Baris et al. found an overall excess (RR 1.7; 0.9-3.1) increasing with duration of employment, with 20+ years having a borderline statistically significant SMR of 2.31 (1.0 – 5.2), and a statistically significant SMR of 2.54 (1.2-5.7) for engine company employment only, with some suggestion of correlation with medium and high diesel exposures (latter based on small numbers of deaths).[11] This pattern is suggestive of a strong association that cannot be dismissed as confounding. However, the NIOSH Study, which did not examine specific jobs, did not find an elevation overall or in any subgroup or city, including Philadelphia.[47]

The weight of direct evidence suggests that myelomas and cancers in this category (it is a large and complicated rubric) can arise from occupation as a firefighter, but it is entirely unclear which and it is possible, given the biology, that more than one or even all could be. Giving the benefit of the doubt to the worker, as required, the preponderance of the thin evidence favors causation and sufficient weight to derive a presumption. This is also consistent with the recommendation for non-Hodgkin's lymphomas, some of which, particularly the more common B-cell lymphomas, overlap with myelomas biologically and therefore possibly in causation.

The latency period for myeloma appears to be very long in most case, but without a clear causal relationship from which to mark the beginning of exposure it is unclear how one could accurately measure it. The minimum latency is unclear.

Interpretation

The weight of evidence for lymphatic cancer of the non-Hodgkin's type and haematopoietic cancer suggests that the elevation in risk reflects a true risk in certain subgroups but these subgroups cannot be readily identified by usable criteria in adjudication. So far, the weight of evidence suggests that AML, DLBCL, and follicular lymphoma in a firefighter are more likely than not to arise out of their work. Likely candidates among fire smoke exposures have been identified for which the evidence is strong, including human studies. Because the other individual disease risks cannot be separated using current knowledge, they must be taken as a group until more information becomes available.

Lung Cancer

Lung cancer has been the most difficult cancer site to evaluate in epidemiologic studies of firefighters. Lung cancer presents a different problem because the risk associated with occupation is overwhelmed by the effect of cigarette smoking. The evidence suggests that an association does exist but it is likely to be heavily obscured by confounding factors and may not be as strong as would be suggested by the toxicological literature. Confounding among firefighters is also not straightforward, as it reflects past patters of tobacco use. Without question, this complicates the analysis, as discussed in detail earlier in this report. On the other hand, as an example will show, the confounding effects may be exaggerated.

The only unequivocal increase in lung cancer observed to date comes as preliminary data from the Nordic study, which is not yet available in its entirety and has been described only in abstract, provides evidence for a significant elevation of incidence for adenocarcinoma of the lung (SIR 1.31, 1.04 – 1.63), but not other tissue types.[154] This presents an interpretive problem because adenocarcinoma is the characteristic tissue type seen in non-smokers and in persons exposed to passive cigarette smoke, although the frequency is also elevated in smokers. This suggests that in this context fire smoke might be behaving similarly to sidestream cigarette smoke rather than mainstream cigarette smoke. However, this must remain speculative until more information is available and the finding is confirmed.

Despite the obvious exposure to carcinogens inhaled in smoke, as described in detail earlier in this report, it has been difficult to document an excess in mortality from lung cancer of a magnitude and consistency compatible with occupational exposure. Municipal fighters entering the fire service in Alberta from 1927 to 1987 show some evidence for an increase in risk overall and by duration of exposure, but the trend for the first two decades is not smooth or significant, the elevation falls off after 20 years, and then becomes marked and significant after 35 years. but suggests a high risk for new hires and firefighters who may not have completed their probationary period satisfactorily.[12] The trend may be heavily confounded by smoking and by era but it could also suggest that duration of firefighting is only part of the picture and that susceptibility plays a role both in early incidence and in resistance, survival, and later incidence. Respiratory protection has reduced individual exposure levels to combustion products since the 1970's, and this may be the

reason that studies rich in recent person-years of observation, such as Baris et al , do not observe such elevations.[11] On the other hand, Ma et al., who describes no elevation in risk for male firefighters in Florida, found the usual moderately elevated risk (SIR 1.40; 0.28-4.08) for females, who in general entered the fire service so recently relative to men that most or all the required latency would not have expired.[75]

On the other hand, the prevalence of smoking among contemporary fire fighters does not appear to be excessive compared to other "blue collar" occupations, in the 1990's as they do now.[155,156] It is estimated from recent data in the central states of the US that approximately 13.6% of professional firefighters smoke, less than the 21% of the general adult population and much less than the 29% prevalence of comparably highly-paid, highly-skilled blue-collar workers. Firefighters, at least in North America, appear to smoke less even than the 20% prevalence of white collar workers, who are usually taken to define low-risk groups for lung cancer and other smoking-related disorders.[155,157] Therefore, the proportion of their lung cancer burden attributable to occupation as a firefighter is likely to be higher.

A comparison that takes into account the prevalence of cigarette smoking is illuminating.

Population Risk Attributable to Fire fighting

Many studies have shown an excess of lung cancer on the order of 20 to 80% (i.e. SMRs around 120 or 180), a magnitude not uncommon in studies of other blue collar occupations with less plausible exposure levels.[158] LeMasters, summarizing the literature to 2006, found no elevation.[5]

However, the empirical findings on lung cancer from recent, well-designed epidemiological studies have been inconsistent.[79] One study from Denmark reported a standardized mortality ratio of 317 for older fire fighters but the comparison population was unusual and difficult to interpret.[159.] Studies on cohorts from San Francisco[18] and Buffalo[160] showed no excess and even suggested a deficit, as do most of the population monitoring studies (which systematically tend to underestimate risk, and so are not cited in this section).

On the other hand, the NIOSH Study, with its large number of subjects and power, showed a statistically significant overall elevation for both mortality and incidence (SMR 1.10; 1.04 – 1.17) a remarkably consistent across almost all subgroups, except for no elevation among non-Caucasians.[47]

There are contextual reasons for thinking that the true risk has been underestimated in career firefighters. All but a few extant studies that are positive, relevant, close to the primary data, large and well done seem to cluster in a band from an excess of 30% to 68%, as can be seen in this report.[79] The principal exceptions are Baris et al.[11], and Vena and Fiedler[160]. Baris et al., despite a low overall risk (1.13; 0.97 – 1.32) does report suggestive elevations in certain subgroups, notably fire fighters with less than 9 years of service (1.52; 1.16 – 2.01), those assigned to engine companies (1.18; 0.93 – 1.51), and those hired before 1935 (1.30; 0.97 – 1.73). Vena and Fiedler present one of the lower overall risks in the fire fighting literature (0.94; 0.62 – 1.36) but their data show a possible exposure-response relationship with duration of employment (a near-monotonic increase of 0.14 relative risk for each of five decade of fire service, nonparametric $p < 0.07$) and a statistically significant excess (at $p < 0.01$) for fire fighters with more than 40 years of fire service (1.29). (Vena and Fiedler also compared their incident cases to the "general population", however, in that era Buffalo residents already had one of the highest mortality rates of cancer in the United States.[161]) Heyer et al.[145] reported an overall risk of only 97 (65-139) but observed an elevated risk among fire fighters aged 65 years or more, when the incidence of lung cancer tends to peak. Thus, even in so-called "negative" studies there are hints of a possible association.

Among those studies that appear to be unequivocally "negative", Beaumont et al.[18] reports the lowest risk (0.84; 0.64 – 1.08). This same study is unusual among the major studies because it also shows the largest healthy worker effect, the lowest overall mortality from all causes 0.90 and the lowest mortality rate cancer (0.95) an atypical age distribution and a high rate of cirrhosis.

At the other extreme is Hansen et al.[159] in which an overall risk of 163 (75 – 310) was accompanied by a tripling of risk (SMR% 317) for firefighters aged 60 to 74. This was an imaginative Danish study that aggregated other occupational groups into a synthetic reference group. However, the artificiality of this construct makes the study difficult to interpret.

In our study of urban fire fighters in Alberta[12], we found trends that we believe suggest a true SMR% on the order of 150 in that population. Individually, these trends are not definitive but together they are highly suggestive. The overall SMR% for lung cancer was 142 (95% confidence interval (91, 211), statistically not significant, and statistically indistinguishable from 150. However, lung cancer was elevated to an SMR% of 167 among fire fighters entering the fire service in the 1960's, the most recent cohort at the time of the study for which the expected latency period had elapsed. This is not strong evidence, because it is based on only two cases, but the following cohort

of firefighters entering in the 1970's showed an even greater risk, 261 (although based on a single case). The risk of lung cancer also showed an exposure-response relationship in our data, with groups of fire fighters who had higher exposure opportunities and duration showing elevations on the order of 200. By duration of employment, an initially high risk for those with less exposure declined with duration of employment but achieved a doubling for those working 40 or more years (although only two firefighters were in that group). More persuasively, when duration of employment was corrected for exposure opportunity in job classification, the exposure-response relationship changed to suggest, following an initially high risk among probationary fire fighters or those unfit for duty, a more or less consistent but low elevation for the middling exposed varying around 150 (range 32 to 258), and a significantly elevated risk (408, $p < 0.05$) for those with more than 35 exposure opportunity-weighted years of employment.

Unfortunately, the data from other studies cannot be disaggregated on the same basis as the Alberta cohort. Even so, Baris et al[11] , although negative overall, appears to show the same effect in the first 9 years.

An important factor in the Alberta study, which was not appreciated at the time of initial publication, is that cigarette smoking is historically less of a confounding factor in Alberta than it has been in other populations.[162] Subsequent studies of smoking-related lung disease outcomes suggest that smoking rates have been historically low in the province compared to the rest of the country and this is reflected in lower mortality from chronic obstructive pulmonary disease. In recent years mortality rates for smoking-related disorders appear to have converged with the rest of Canada as smoking rates in the rest of the country have gone down and those in Alberta have changed less dramatically. This suggests, but does not prove, that the Alberta experience is less confounded by cigarette smoking than elsewhere.

An anomaly of the Alberta data is that the excess was seen in one city (Edmonton) and not another (Calgary). In Edmonton alone, the risk was 201, the highest overall risk for lung cancer reported.[12] The two cities represent an internal replication because the same study team collected data from both cities following the same protocol, matched against death certificates concurrently and analyzed both data sets simultaneously.

By a mathematical manipulation of the known data, it has been proposed that compared to nonsmokers as a group, nonsmoking firefighters are estimated to have much more than a doubling of risk compared to other people who do not smoke.[7] The exact value is unimportant

because of the compounded uncertainties; that it clearly exceeds a doubling is what matters most. This derivation suggests that the risk of lung cancer in a non-smoking firefighter is more than doubled (estimated to be about 3.3) compared to the general population of non-smokers, making allowances for great uncertainties. This suggests that exposure within the profession of firefighting is important and, making allowances for uncertainty, triples the risk of lung cancer in a person who would otherwise have a very low risk. An elevation of three-fold is a large risk for an occupational hazard.

Smoking and Firefighting

It is well established to the point of being a convention to accept 20 American pack-years (equal to 16 Australian pack-years) of smoking (pack-years represent the total number of packs per day multiplied by the number of years a person smokes at that level) as the point at which lung cancer risk begin to rise noticeably and exponentially. Note that this is not a threshold for toxicity, as there is a measurable risk below that and there is no safe level of cigarette smoking. It is simply the inflexion point at which the risk curve takes off for the population and becomes significant against the background of other causes of lung cancer. However, smoking history is confounded by age, since years as a smoker are years lived, and after about age 50 (noticeably after 55) the risk of lung cancer among smokers rises as a power function.

It should be noted that, paradoxically, cigarette smoking exposure is more potent per unit smoked at low intensities of smoking, meaning that the risk *changes* more dramatically at levels below one half-pack per day than at heavier smoking levels, but the overall excess risk is still higher with cumulative exposure, with longer duration and intensity. As a practical matter, this means that a cigarette smoking habit of about 25 years' duration probably roughly matches the risk from firefighting but that above that level cigarette smoking becomes much more of a driver of cancer risk and overwhelms the firefighting effect, rendering it negligible compared to smoking.

Whether the additional risk from firefighting contributes substantially to the overall risk depends on what is deemed to constitute a substantial contribution. Certainly, one could make a case that at 20 (Australian) pack-years, firefighting is still contributing a significant amount of risk, which, if apportioned in a "typical" individual taken from this population, might be about

half of the risk of lung cancer (recognizing great uncertainties and individual factors). In such a situation, perhaps half of firefighters who smoked at that level would not have developed cancer "but for" their work as a firefighter. Above that level of smoking, however, the risk from smoking dominates, making the relative contribution from firefighting small.

It might be argued that, like other carcinogens, cigarette smoking and other exposures arising from firefighting (fire smoke and diesel exhaust) are positively interactive (or "synergistic") and cause more lung cancer than would occur otherwise. This is possible but unlikely, because fire smoke and cigarette smoke are products of combustion and mostly contain the same carcinogenic chemicals, particularly polycyclic aromatic hydrocarbons and nitrenes, and other carcinogens including vinyl chloride and benzene.

However, interaction cannot be ruled out because the smokes are not exactly alike. Fire smoke contains much higher levels of trichloroethylene (a carcinogenic solvent chemical) and cigarette smoke contains a radionuclide (^{210}Po), among other differences. Cigarette smoke inhalation does not carry the risk of exposure to asbestos and to diesel exhaust (a more potent source of nitroarenes) but firefighting clearly does. Also, as noted, cigarette smoke has anti-inflammatory activity that fire smoke does not appear to demonstrate. These differences mean that fire smoke and cigarette smoke (and for that matter fine particulate air pollution) cannot be equated in their toxicity, and may show substantial differences. Fire smoke, although generally simpler but still complex, contains a variety of compounds not found or are found in less concentration in cigarette smoke, including trichloroethylene and other chlorinated hydrocarbons.

It is much more likely that the relative contribution to risk of cigarette smoke and smoke inhaled during firefighting are proportionate to exposure on a simple additive basis (considering exposure level). In this situation, the toxicological properties of the smoke are similar and act by the same biological mechanisms, the contribution to risk will be additive, not interactive (synergistic). Smoking habits are variable but the average smoker almost certainly inhales smoke for a longer total time period during the day than the average firefighter does during the course of an average working day. Cigarette smoke is also inhaled directly from the source and so is less dilute than most (by no means all) opportunities to inhale fire smoke.

However, it should also be emphasized that this argument applies only to lung cancer, not to deep cancers. Although similar, cigarette smoking is not identical to fire smoke. Cigarette

[redacted]

smoke, as a complex mixture, also contains some poorly characterized anti-inflammatory agents that suppress the potential acute irritation, which may in part explain why people tolerate the irritation to airways. Cigarette smoke contains many constituents that act locally to induce cancer. One of the most important, as noted, is thought to be polonium, ^{210}Po, which is accumulated by the tobacco plant). It is deposited directly onto applied to the pulmonary epithelium and does not undergo prior metabolic transformation. In deep organs, smoke constituents are mostly pre-metabolized (locally, in the liver, or in the lung).

Even so, the argument for a difference in the effect of the two smokes is more convincing for respiratory effects than for carcinogenicity. The evidence suggests strongly that cigarette smoking is likely to be at least as potent as fire smoke and usually more concentrated when inhaled, and exposure clearly occurs more frequently among smokers,. In that case, the effects are much more likely to be additive and proportionate to the cumulative carcinogenic exposure.

Mesothelioma

For many years firefighters have sought recognition of their exposure to asbestos as an important hazard but this has been difficult to substantiate because the characteristic signs of lung diseases due to asbestos (mostly chest film findings) are not frequent on chest films of fire fighters. (There is no proper study, but numerous opportunities to have made the observation.) This has now been accomplished with the demonstration in two studies of an elevated risk of mesothelioma in firefighters.

Mesothelioma is a distinct cancer of the lining of the thoracic or abdominal cavities (the pleura and the peritoneum, respectively). It is caused by asbestos exposure, almost exclusively. Some cases are associated with fibrous (asbestos-like) naturally-occurring minerals called zeolites (mostly erionite). It is controversial whether mesothelioma ever occurs without exposure to an asbestos-like agent, but if it does this is exceedingly rare.

Exposure to asbestos is likely to occur when firefighters engage in cutting into structures and in overhaul, when asbestos-containing materials are present. This is most likely to occur in fighting fires in older buildings, including houses, in recent years especially those that have not been renovated or remediated.

The NIOSH Study demonstrates a significantly elevated risk for overall mortality (2.00; 1.03 – 3.49) and incidence (2.29; 1.60 – 3.19), and in all three cities (Chicago and Philadelphia and elevated but not statistically significant in San Francisco).[47] This is entirely consistent with asbestos-containing materials present in older housing and building stock.

The Nordic Study, for which details are still not available, the overall risk of mesothelioma was elevated (SIR 1.56; 0.91 – 2.50) and significantly elevated among firefighters over 70 years of age (SIR 1.56; 1.25 – 4.56).[154] The latency period for mesothelioma is variable but tends to be very long; four or five decades is not unusual. Firefighters currently at or older than age 70, if they entered the fire service in their twenties or thirties, could have been exposed outside the fire service in the 1960's or 1970's when asbestos was still used in construction, in addition to exposure during their tenure in the fire service. However, the persistence of the elevation in firefighters younger than 70 strongly suggests that their relevant exposure occurred mostly or exclusively on the job, because asbestos was removed almost completely and abruptly from commerce in developed countries in the 1970's, particularly in Scandinavia.

Therefore the weight of evidence strongly favors the conclusion that mesothelioma is an occupational disease of firefighters.

Colon and Rectal Cancer

Lemasters et. al.[5] demonstrated a significantly elevated risk of approximately equal magnitude for both colon cancer (summary risk 1.21; 1.03 – 1.54) and rectal cancer (1.29; 1.10 – 1.51). Individual studies vary, with some (Demers 1992) showing no elevation in either.[144]

The literature generally supports the conclusion that there is an increased risk of colon cancer among firefighters in general but not that this increased risk equals or exceeds a doubling, which would correspond to the criterion of "more likely than not" in the individual case. Recent studies, including thorough and detailed work of high quality such as Baris et al., although showing variability common in such occupational studies, have not refuted this conclusion and have strengthened the evidence for an association both by replication and by demonstrating a dose (exposure)-response relationship (in the Baris study).[11]

Overall, Baris et al. found an SMR of 1.51 (1.18; 1.93), based on 64 deaths; there was no consistent dose-response for duration of employment or for cumulative number of runs.

[redacted]

However the risks were greater than 1.00 for all three levels, 1.93 for low; 2.22 for medium and 1.22 for high number of runs. Elevated colon cancer risk has been reported in many other studies.[136, 141 192]. Schwartz and Grady, who examined occupational associations of colon cancer in New Hampshire in the 1980's,[163] and Vena and Fiedler in Buffalo[160] reported a significantly elevated SMR of 1.83. Thus, two old studies, one in two out of three subgroups and the other in the population as a whole, have demonstrated elevated risks. Although not as easily demonstrable, it may be argued that claims for colon cancer may be justified in the same way as for lung cancer in an individual with a low *a priori* risk for the disease.

Kang, using a methodology that tends to underestimate risk, observed a statistically significant excess when compared to police (SMOR 1.36; 1.04-1.79) but not another referent population (SMOR 1.15; 0.93-1.43).[112]

Ahn et al.[113] demonstrated an overall elevated risk for cancers of the colon and rectum among Korean emergency responders, who serve multiple roles but are engaged in active firefighting. This large study based on the national cancer registry, which as noted seems likely to be biased toward an underestimate, demonstrated an elevated standardized incidence ratio for colorectal cancer (SIR 1.35; 1.07.1.67).

The NIOSH Study reported a consistent and significant elevation in colon cancer (SMR 1.31; 1.16 – 1.48, SIR 1.28; 1.09 – 1.43), consistent across racial groups and showing a small monotonic increase in the first three (out of four) decades of employment duration.[47] Similarly, the same overall pattern was observed for rectal cancer with fewer numbers, without a clear duration-response relationship and with some associations not achieving statistical significance, (SMR 1.45; 1.16 – 1.78, SIR 1.11; 0.95 – 1.30). Neither were compared by city.

Rectal cancer shares the same risk factors as colon cancers but also features additional known risk factors associated with lifestyle. Many authors emphasize the differences in the risk factors associated with colon and with rectal cancer and suggest that this is an obstacle in accepting colorectal cancer rates in defined occupations. Their interpretation is that studies that combine risk for colon and rectum do not reflect occupational risk factors for colon cancer overall. Several studies (Kang, Burnett[88]), are also notable for showing a wide discrepancy between colon cancer, which is significantly elevated, and rectal cancer, which less often elevated. It is likely that non-occupational risk factors, as well as random variation, are driving the differences. However, this argument is not entirely valid because a divergence in the two

cancer sites would require a difference in distribution of risk factors among firefighters that is not observed in the general or reference population.

Rectal cancer shares with colon cancer almost all known risk factors for colon cancer alone, not unexpectedly. There are indeed additional risk factors that increase the risk for rectal cancer alone, all of which relate to lifestyle among certain subgroups defined by sexual preference and practices. These lifestyle risk factors appear to be relatively small in their overall population effect, compared to other risk factors for colon cancer. To confound the risk estimate for firefighting as an occupation, these subgroups would have to be substantially more frequently represented among firefighters than in the general population. There is no evidence or reason to believe that this is the case. Furthermore, recent studies by the National Institutes of Health have demonstrated that the biology of colon and rectal cancers is the same, in terms of gene upregulation. Colon and rectal cancer are therefore the same disease biologically, appearing at different locations in the gastrointestinal tract, with additional risk factors for rectal cancer as a result of lifestyle and anatomical location (more subject to irritation).

A prospective study attempted to detect rectal and sigmoidal polyps in less than 200 firefighters in Phoenix (Arizona) over seven years in the 1988 to 1995. On the basis of unremarkable findings and no carcinomas found, the author concluded that there was no elevation in risk. However, this study did not meet contemporary standards for cancer surveillance studies: there was no reference group, the study population was tiny, no power analysis was performed, and the method of detection, sigmoidoscopy, was inadequate in that it does not visualize the full colon. This study, which was only reported in abstract, should carry little weight in review.[164]

Youakim[4] concluded on the basis of his meta-analysis that the risk for colon cancer among firefighters was significantly elevated, appearing after 30 years of service, and was highest after 40 years.

Thyroid Cancer

Thyroid cancer is a relatively uncommon cancer the most common forms of which are easily treated and seldom fatal. It is therefore not usually observed to be elevated in mortality studies. There is no obvious exposure in firefighting that would be associated with thyroid

cancer. Elevations have only been noticed recently in studies of firefighters, but this is more likely due to the application of different methods than it is to reflect trends over time. Thyroid cancer might be affected by screening bias favoring detection of cases in individuals with better health care, since it is possible to have asymptomatic thyroid cancer.

The study by Ma et al.[75] of Florida firefighters contained the striking observation that cancer of the thyroid is markedly and statistically significantly elevated in incidence for both male and female firefighters (SIR male 1.77; 1.08-2.73; females 3.97, 1.45-8.65).[110] As yet, these findings have not been duplicated. Thyroid cancer appears separately in this study and not others presumably because the measure was cancer incidence study rather than mortality. Kang in the study of Massachusetts firefighters, did not observe an excess but that study had much less power.[112] The NIOSH Study (Daniels 2013) showed no elevation for thyroid cancer overall or by city.[47]

As yet, there is insufficient evidence to make a recommendation but if future studies demonstrate an elevation of similar magnitude, thyroid cancer may be considered an occupational outcome among firefighters on the basis of consistency and the strength of the association, despite the absence of a known mechanism.

Head and Neck Cancers

Head and neck cancers have often been overlooked or aggregated in firefighter studies. Head and neck cancers tend to be individually uncommon, do not form a logical rubric, and are easily misclassified. Head and neck cancers, in general, are associated with risk factors involving location (sunlight exposure, especially for for lip), comorbidity (previous treatment for cancer, radiation), lifestyle (smoking, smokeless tobacco usage), and occupational exposures (wood dust, agriculture). Individual head and neck cancers have particular risk factors as well. These cancers tend to be highly disfiguring and dreaded, so they have received considerable attention. Because of numerous shared risk factors, this are a more useful aggregation than most because they share such a remarkable number of common risk factors.

Lemasters in her meta-analysis suggested an overall elevation in the literature to 2006 (summary risk 1.23; 0.96 – 1.55).[5] However, this meta-analysis did not take individual sites into

consideration. For a heterogeneous collection of cancers, this may be less of a problem for head and neck than for other rubrics because the many head and neck cancers share many risk factors.

Cancer of the lip was noted to be highly elevated by Beaumont[18] but not significantly due to low numbers (RR 6.17; 0.75 – 22.29, two cases) and significantly elevated by Sama (1998) (MOR 5.9; 1.9 – 18.3) although the number was very small (three).[150]

Oral and pharyngeal cancers are mostly squamous cell cancers, with known associations with smoking, smokeless tobacco, alcohol abuse, cocaine abuse, nickel subsulfide exposure (not a hazard of firefighting), welding fumes (preliminary), radiation, betel nut chewing, regular consumption of Chinese salt-cured fish, lichen planus (a disease of the mouth), and infection with Epstein-Barr virus or HPV16 (a human papillomavirus that often populates the female genital tract). None of these are plausible hazards associated with firefighting. Most of the few studies of firefighters that do break out sites in the oral cavity and pharynx have not shown an elevation with some conspicuous and noteworthy exceptions. Individual studies vary in reported risk, with Aronson/L'Abbe 1992 showing a non-significant elevation in risk of pharyngeal cancer (SMR% 139) increasing with years since first exposure (which conflates latency with exposure duration).[165] Demers showing a modest deficit in oral and pharyngeal cancers (SMR 0.81; 0.33 – 1.66).[126,144] Baris found an elevated risk (SMR 1.36; 0.87 – 2.14) for the buccal cavity and pharynx.[11] Kang found no elevation in cancers of the buccal cavity and nasopharyns.[112]

Cancers of the salivary glands, including the parotid gland (in the cheek), were not separately examined in most studies but became an outcome of interest after Ahn demonstrated a high but not significantly elevated incident risk based on very small numbers for Korean firefighters (SIR 2.34; 0.47 – 6.83, three cases) with no association with employment duration, but not seen in non-firefighting emergency medical technicians in the same departments.[113] This group was also somewhat elevated for white firefighters in the study by Ma (1998) at MOR 1.3 with only 3 cases). Parotid gland tumors are known to be associated with Sjögren's syndrome (dry mouth), radiation exposure, and exposures in the rubber industry (thought to be dominated by nitrosamines), none of which is likely to apply to firefighting. Why the parotic gland would be so susceptible is not clear.

Cancer of the nasal sinuses would be expected to be associated with firefighting because smoking is a risk factor and "coarse" (relatively large) particulate matter such as wood dust tends

to be retained in these locations. Surprisingly, given the likely exposure of firefighters to wood dust and coarse particulate matter carrying PAHs, cancer of the nasal sinuses has been separately investigated only once, by Demers (1994) in a three-city study, which found an elevation based on very small numbers (SIR 2.12; 0.1 – 12.4, two cases).[126].

Laryngeal cancer might be expected to be associated since the vocal apparatus is in a vulnerable position for exposure to inhaled carcinogens and cancer of the larynx is associated with cigarette smoking. Cancer of the larynx shares many risk factors with lung cancer, including asbestos, with the additional risk factor of alcohol abuse. LeMasters found a summary risk estimate of 1.22 (0.87 – 1.70). Several studies have shown a deficit for firefighters individually.[18,106,126]

The NIOSH Study (Daniels 2013) did not examine head and neck cancers.[47]

Breast

Meta-analyses have not been conducted for this site because few or no early studies looked at male breast cancer, specifically.

Male breast cancer has attracted attention in recent years because of several high-profile cases among firefighters. The Supreme Court of Nevada (which admittedly has limited relevance to the Commonwealth of Australia and its states) has ruled that a woman firefighter was entitled to presumption for breast cancer as arising out of work as a firefighter, in January 2011, on the basis that firefighting exposed workers of both sexes to chemical carcinogens. (The court unfortunately focused on benzene as the putatively responsible carcinogen, which is unlikely but could serve as a surrogate for exposure to the many and varied other fire-associated carcinogenic exposures.) The Court is quoted as opining "despite the limitations of some of the studies, we conclude that a reasonable person could have found from the totality of the evidence presented at the hearings that the benzene (the firefighter) was exposed to was reasonably associated with breast cancer." The emphasis on totality of evidence and "a reasonable person" (implying weight of evidence) is similar to the framework described in the 1995 and the 2005 papers cited above.

Ma (2005), evaluating risk of death (mortality) by cancer among firefighters in Florida, found a highly and highly significantly elevated rate of male breast cancer (SMR 7.41; 1.99 - 18.96).[75] There appears to be some early evidence of convergence in risk between male and

female breast cancer among firefighters, but the data to date are preliminary. There was also roughly a doubling of risk for female firefighters, but based only on a single case, because of the small number of women firefighters.

Kang found an elevation of 1.28 (1.00 being equivalent to the reference population) compared to all occupations reported in the Massachusetts cancer registry, and 0.25 compared to police.[112] The risk was 0.42 for the age group 55 to 74, the only age category for which there was sufficient data to make any estimate. This is entirely explicable by the rarity of the cancer and the very low likelihood of any one study demonstrating the true risk. The same is true for other etiological studies of cancer in firefighters, few of which examine male breast cancer separately. (Kang, in 2008, followed Ma's 2005 study, and so their team looked for it specifically because Ma had already reported it.)

The NIOSH Study (found an elevation in mortality and incidence for male breast cancer ((SMR 1.39; 0.60 – 2.73 with eight cases, SIR 1.26; 0.82 – 1.85,with 26 cases), with no data on subgroups.[47]

In the United States, breast cancer among men is exceedingly rare, at about 1 case per 100,000 men per year, a rate that may be increasing slowly. Male breast cancers comprise much less than 0.5% of cancers in men overall in the US, although rates are much higher in some parts of Africa. The strongest risk factor for male breast cancer is age, and most cases occur in men over age 65. When it does occur, the tissue type for male breast cancer is "infiltrating ductal carcinoma", which should not be confused with the relatively slow-growing "intraductal" type that has been diagnosed increasingly among women with near-universal use of mammography. Male breast cancer is normally estrogen-sensitive.

A large study of male breast cancer incidence in the United States that was published in 2004[166], early in the current debate on the efficacy of screening, determined that there is increasing frequency of detection of the disease, although not to the same degree as for women, and that it is more often detected at older age, after having already developed metastases, and at a larger tumor burden. However, for a given stage of the disease, survival was similar between male and female breast cancer. Because it is detected at a later stage, male breast cancer overall, without adjusting for stage, has a poor prognosis, which makes mortality an accurate surrogate for incidence. This is important for the validity of statistical studies because it means that mortality (rate of death) is a reasonable surrogate measure for incidence (rate of new or newly

detected disease) for male breast cancer and that elevated mortality tracks along with elevations in incidence in men. (It does not in women.)

It is assumed that male breast cancer and female breast cancer share some risk factors but not others. Female breast cancer is associated with nulliparity (not giving birth) and the absence of lactation, obesity (thought to be possibly due to diet and metabolic changes associated with it, but probably not obesity as such), and older age at giving first birth. These factors probably do not apply to male breast cancer. Female breast cancer risk is known to be associated with estrogen stimulation and is strongly suspected to be associated with exposure to chemicals that mimic the effects of estrogen. Female breast cancer risk is also associated with exposure of the breast to radiation. The male hormonal risk factors associated with breast cancer risk are those associated with increased estrogenic activity, such as testicular failure, gynecomastia, infertility, and significant alcohol abuse (presumably mediated through reduced clearance of estrogen by the liver). Female breast cancer is not associated with cigarette smoking, so there is no *a priori* reason to suspect that this would be a factor in male breast cancer either.

There are four plausible explanations that apply to general causation in male breast cancer.

The single most likely explanation is that firefighters are exposed regularly to products of combustion, including potent carcinogens listed above, that are relatively non-selective. In other words, they may cause cancer in bladder, kidney, or lung depending on where the chemical interacts with DNA, acting randomly at the cellular level in tissues. Male breast cancer is probably no different in its susceptibility to these carcinogens but because there is very little breast tissue in men, cancers from exposures to carcinogens that cause cancers elsewhere in the body arise much less frequently there than from those other tissues.

The second-most likely explanation may be that because male breast cancer is estrogen sensitive and estrogen-receptor positive, and because men produce relatively little endogenous estrogen to compete with estrogen activity-mimicking toxic agents, breast tissue in men respond to stimulation from estrogen-like chemicals. (This is demonstrated periodically in outbreaks of adult gynecomastia, a disorder in which men grow excess breast tissue, caused by occupational exposure, such as one particularly well-studied case among pharmaceutical workers packaging birth control pills at a factory in Puerto Rico.) Among the combustion products to which firefighters are exposed are numerous polycyclic aromatic hydrocarbons and chlorinated

polycyclic hydrocarbons (among them dioxins) that resemble estrogen structurally and are known to have some degree of estrogenic activity, although it is much less than estrogen itself.

Another plausible explanation is the effect of shiftwork, which is known to be a risk factor for female breast cancer and for which there is a well-developed, plausible explanation involving disruption of circadian rhythms and hormone cycles that are associated with breast cancer. The net effect is to make breast tissue more susceptible to cancer initiation in the individual. This explanation has been accepted for female breast cancer by IARC. It would logically apply as well to male breast cancer.[127]

The last somewhat plausible explanation is that electromagnetic fields induce cancer in firefighters surrounded by radio transmission and electronic equipment, a theory espoused by Dr. Samuel J. Milham but that has not gained wide support.[104]

Skin Cancer (including Melanoma)

Melanoma is a skin cancer that is usually highly malignant (often metastatic or invasive when discovered) and is frequently fatal despite treatment. Melanoma shares with other skin cancers, mostly squamous cell carcinoma and basal cell carcinoma, various risk factors, including vinyl chloride (which is present in fire smoke), PCBs, possibly solvents and arsenic. However, the most important shared risk factors of skin cancer are electromagnetic radiation, both ionizing and, predominantly, ultraviolet radiation. However, while the other skin cancers show an exposure – frequency relationship that seems to be cumulative (reflecting total skin damage), melanoma appears to correlate more closely with discreet events of sunburn at a young age, suggesting that acute damage followed by healing contributes to risk.

Melanoma was identified as elevated by Lemasters in the literature up to 2006 (summary risk 1.32; 1.10 – 1.57).[5] Feuer (1986) demonstrated a significantly elevated risk of 2.70 against US white males and a elevated risk of PMR 1.90 against local, New Jersey white males.[76] Bates demonstrated a statistically significant elevation for melanoma among California firefighters (OR 1.50; 1.33-1.70).[167] The NIOSH Study does not suggest an elevation for skin cancers (mortality from which would be associated with melanoma).[47]

As well, a multicentre case-control study of occupation and non-melanoma skin cancer among Spanish firefighters found a large but not quite statistically significant elevation in risk for basal cell carcinoma among firefighters (RR 4.55, 0.96 – 21.57).[168]

Firefighters are obviously exposed to carcinogenic chemicals present in fire smoke that are active in causing skin cancer, chief among them PAHs, but are unlikely to be exposed to arsenic or ionizing radiation. The role of chemical exposure is difficult to sort out mainly because of confounding from ultraviolet radiation.

By far the most plausible exposure responsible for elevated melanoma (or other skin cancer) rates would be exposure to ultraviolet radiation outdoors, in which case one might expect that the elevation would be higher among wildfire fighters, who work outdoors for longer periods than urban firefighters. That does not seem to be the case, as reflected in studies of wildfire fighters alone, but the issue has not been separately addressed.[45] One might also expect turn-out gear to be protective against ultraviolet exposure, since it covers most of the body. On the other hand, much and probably most exposure to ultraviolet radiation occurs in recreational and other non-occupational settings. The highest risk for melanoma appears to be from episodes of acute sun damage occurring early in life and in young adulthood, a causal model that does not fit well with firefighting, but could fit with lifestyle factors.

Thus, an association of melanoma with firefighting based on ultraviolet exposure would appear unlikely for municipal firefighters but likely for wildfire fighting where deployment is for prolonged periods, sun protection is not provided by turnout gear, and associated with camp living and outdoor work without protection. On the other hand, melanoma risk is empirically elevated among firefighters in general and there are plausible, if not persuasive, associations for it aside from ultraviolet exposure.

Other Cancer Types

Elevations in risk have been found in other cancer types but so far without confirmation or replication. Except where noted, few studies have reported information needed to apply the appropriate analytical methods to these cancers. Rather than cite individual studies prior to 2006, therefore, the summary risk estimates of Lemasters are used as a guide to the general trend of evidence.[5]

Esophageal cancer was determined in the meta-analysis of Lemasters (2006) to be elevated in the literature up to then at (summary risk 1.16; 0.86 – 1.57). Bates also demonstrated a statistically significant elevation for esophageal cancer among California firefighters (OR 1.48; 1.14-1.91).[111] It is difficult to identify a plausible exposure that could be responsible, although nitrosamines (more familiar as dietary risk factors) are formed by combustion. The NIOSH Study demonstrated an excess risk of both mortality and incidence (SMR 1.39; 1.14 – 1.67, SIR 1.62; 1.31 – 2.00) with a marked between racial groups (Caucasians 1.46; 1.20 – 1.75, non-Caucasians 0.51; 0.11 – 1.49) and no duration-response relationship.[47] The known risk factors for esophageal cancer include esophageal reflux disease (Barrett's esophagus), alcohol intake, smoking, obesity, consumption of pickled vegetables (in Asia), consumption of scaldingly hot tea, and exposure to silica (well documented) and asbestos, the latter rather speculative. It is unlikely that these risk factors would be so prevalent among firefighters, specifically, as to lead to an elevation in risk for this cancer. Stronger associations are found for socio-economic status, location, and lifestyle. At present this isolated finding cannot be adequately evaluated for firefighters.

Laryngeal cancer was not identified as elevated by Lemasters in the literature up to 2006 (summary risk 1.22; 0.87 – 1.70) but incidence studies, which may be a truer indication for a surgically curable cancer, showed higher risks than mortality studies, with wide confidence intervals and without achieving significance.[5] Firth[115] found an astronomical elevation in risk for cancer of the larynx (SIR% 1348; 254-3991) after adjustment for socioeconomic status but no similar finding has been reported in another study. Among the many hazards to which firefighters are exposed, asbestos would be consistent with an elevated risk for laryngeal cancer but the relative infrequency of asbestos-related disease among firefighters overall suggests that this is not the explanation. Still, the commonality with lung cancer suggests that laryngeal cancer risk is likely to be elevated among firefighters but difficult to demonstrate.

Stomach cancer, which is declining in frequency in the developed world, was demonstrated by Lemasters (2006) to show a significant elevation in the literature up to 2006 (summary risk 1.22; 1.04 – 1.44)[5] and elevations individually in Beaumont (1.31; 0.82 – 1.99).[18] An association with stomach cancer is plausible because significant amounts of material are mobilized from the respiratory tract in sputum and swallowed.

Pancreatic cancer was not significantly elevated in the meta-analysis of Lemasters (2006) but some, particularly early studies but also the NIOSH Study, did not separately address this cancer.[5] Elevations with sufficient numbers to consider included Ma (1998), who found a relatively small but significantly elevated risk for white firefighters (MOR 1.2; 1.0 – 1.5) and a doubling of risk for black firefighters (2.0; 0.9 – 4.6), which did not achieve statistical significance with small numbers.[106]

Cancer of the small intestine is very rare, and when it occurs is almost always an adenocarcinoma. Interest was drawn to this site by the demonstration of a non-significant elevation among Korean firefighters by Ahn[113] (SIR 2.46; 0.76 – 5.75, five cases) with no cases among non-firefighters in the same departments. The NIOSH Study (Daniels 2013) did not demonstrate such an elevation. Known risk factors for this type of cancer include genetic disorders (including celiac disease) and conditions of chronic inflammation of the gastrointestinal tract (such as Crohn's disease), diet (red meat and foods that predispose to nitrosamine formation), and possibly smoking (studies vary). This profile does not suggest an elevated risk for firefighters.

Other gastrointestinal or digestive tract cancers have been aggregated in most studies and so organ-specific rates for sites of interest (principally liver, biliary tract) cannot be separated. Those that have separately identified hepatobiliary cancers (Ahn[113], Baris[11]) show no elevation, with the highest risk among them reported by Demers in 1992 (SMR 1.19; 0.44 – 2.59).[144]

IMMUNE DISORDERS, INCLUDING SARCOIDOSIS

Sarcoidosis is a disorder of the immune system, of unknown cause but highly-specific pathology, characterized by the formation of structured aggregates of inflammatory cells, called granulomas consisting of “giant cells”, which are derived from the scavenger cells of the body. In the lung, these granulomas appear in the interstitium, which is the connective tissue between the air space and the blood space. Sarcoidosis can also appear in other organs and can cause liver disease, eye inflammation, and an arthritis, often associated with a characteristic skin rash of the legs.

Scientists have been trying to find out what causes sarcoidosis for about 140 years with essentially no success. The only external agent known to produce the sarcoid raction is an extract of the lymph glands of a person with sarcoidosis (the so-called Kveim antigen), which is not a particularly helpful observation because it cannot rule out infection, immune response, or toxic accumulation and cannot possibly be a mode of transmission. The granulomatous reaction mimics the characteristic response to a persistent antigen in the lung and other organs, although no such antigen has been identified as the cause of the disease despite years of searching. In many ways, sarcoidosis resembles tuberculosis, but no mycobacteria (the class of bacteria that includes tuberculosis) or other infectious agent, for that matter, has ever been found, despite intensive search. The disease most closely resembling sarcoidosis is beryllium disease, caused by exposure to beryllium in the workplace. This has led to extensive research to search for beryllium in the workplace or aberrant reactions to more common metals in the environment that could produce a disease like sarcoidosis. This search has proven fruitless after over a century, and many decades during which hundreds (possibly thousands) of investigators have applied the most advanced methods to the problem.

Sarcoidosis, or at least interstitial lung disease due to sarcoid-like granulomatous inflammation, has been reported to be in excess among firefighters. This presents an interpretive problem. Sarcoidosis is difficult to recognize and requires a biopsy to diagnosis. This means that it is most likely to be recognized and diagnosed in populations with good medical care who are under close scrutiny. People who are not in a surveillance program are likely to have their sarcoidosis missed or diagnosed late. This means that there is a bias in comparing such populations to the general population or to other groups when health care access is different

between them. Unfortunately, this is a common situation in the United States, where health care is tied so closely to employment and the quality of care is linked to occupation. It is not clear whether firefighters have an excess of sarcoidosis or whether their rate of the disease is the true baseline and it is under-diagnosed in "everyone else". It is quite possible that this could be studied in Australia and the matter could be resolved, given the relative lack of barriers to access and the more consistent quality of care.

Sarcoidosis has been demonstrated to be more common than expected among firefighters, with a point prevalence of 222/100,000 among over 11,000 New York City firefighters compared to none observed among 3000 single-assignment emergency medical services personnel.[169] This systematic investigation was based on a registry of cases established after the identification of a cluster of sarcoidosis cases among New York firefighters in 1979.[170] Because sarcoidosis is not a reportable disease and is rarely fatal, comparison or baseline incidence figures from other populations were not available.

Because the exposure regime experienced by WTC responders was qualitatively different from, and additional to, that of regular firefighters, discrepancy in the rates of sarcoidosis among the two groups could provide a clue to the etiology of this puzzling disease. Sarcoidosis has also been observed in a number of WTC responders. Sarcoidosis, affecting approximately one hundred individuals, has been consistently reported by all cohorts within the different programs that follow WTC-exposed individuals.[171,172]

In the first five years post- 9/11/01, pathologic evidence consistent with new-onset sarcoidosis (or a sarcoid-like granulomatous lung disease) was found in 26 NYFD rescue workers, all with intra-thoracic adenopathy and 6 (23%) with additional disease outside the chest.[173,174] Thirteen were identified during the first year post-WTC (yielding an incidence rate of 86/100,000) and 13 during the next four years (yielding an average annual incidence rate of 22/100,000; as compared to 15/100,000 for NYFD personnel during the 15 years pre-WTC and 5-7/100,000 for a male Caucasian population). On the other hand, only 3 of the 26 cases had evidence of restriction, decreased diffusion, or both, and these studies do not account adequately for reporting and detection biases inherent to the compensation and disability claims post-9/11. Similar findings were suggested by studies in 2 other cohorts, The WTC Registry and the NY/NJ WTC Responders.[173,175] The three studies each have surveillance and detection biases that make comparisons among them, and to non-local referent populations, difficult but the consistency of

their findings is impressive. The component(s) of WTC dust responsible for this granulomatous reaction remains unknown as WTC dust has not been shown to contain substances known to produce granulomatous or giant cell reactions, such as beryllium, zirconium or tungsten.

LUNG DISORDERS

Firefighting involves inhalation of products of combustion, toxic materials that happen to be on site, and particles generated by debris from disintegrating structures. Obviously the lung is the organ of first contact and plays a role both as the route of entry for systemically toxic agents, such as carbon monoxide and cyanide, and as target organ for these various insults, either acute or chronic. The first has been obvious and well accepted. Acute effects on the lung itself have now been well characterized. Chronic effects on the lung itself have been difficult to prove until suitable longitudinal studies of pulmonary function became available. It is still remarkable, despite demonstration that chronic lung disease does exist as a risk of firefighting, how little benign lung disease is associated with firefighting considering the extent and severity of the hazards.

One reason for the difficulty in demonstrating chronic effects was that early population studies focused on the question of whether mortality was elevated from chronic obstructive pulmonary disease (COPD) rather than functional endpoints and did not appreciate the time course of acute effects. When functional endpoints were examined, the results were not always interpreted as they would be today. Even in retrospect, however, there is not much to suggest a relationship. One of the few studies of that era to use an index of exposure also did not show an exposure-response relationship, after an initial period likely to represent probation.[12]

Chronic respiratory disease other than lung cancer has not been prominent in population-based studies of firefighters and cohort mortality studies have generally not shown an effect. One apparent exception is a cohort followed in the US Pacific Northwest up to 1980 that was reanalyzed and found to show a healthy worker effect for overall mortality (SMR 82), which has been absent in most studied in that era, and no elevation in mortality from non-malignant respiratory disease (81; 71 – 89) when compared to the US general male population. On the other hand, firefighters were reported to show an excess (SMR 141; 86 - 294) when compared to police. However, in this study police had an unusually low mortality from non-malignant respiratory disease (SMR 48; 25 – 84), compared to the general US population.[176] Thus, it seems more likely that the study is actually uninformative, because of an anomaly in the police, rather than being the strong evidence for an effect among firefighters that the authors suggested.

A more nuanced way of thinking about lung effects was to consider acute and chronic on a continuum of effects.[177] Earlier investigators were not remiss in neglecting this obvious natural history. However, the evidence compiled to test this line of thinking was also initially misleading.

Acute lung injury, as with other toxic effects, should be proportional to exposure, both in terms of peak concentration (which would be expected to correlate with provocation of bronchospasm, and cumulative exposure, or dose, which would be expected to correlate with inflammation and chronic effects. In one particular bad office building fire in Los Angeles burning polyvinyl chloride released clouds of thick black smoke and 19 firefighters demonstrated transient hypoxemia and two who were also involved in fire suppression did not. When they were retested a month later and compared to matched controls, they had returned to baseline lung function, which was within predicted limits for all but four who smoked. This study suggested that the acute lung injury of smoke inhalation was transient and did not lead to immediate de-compensation of baseline function. The authors concluded that acute smoke inhalation did not appear to predispose to the development of chronic respiratory symptoms or chronic functional respiratory impairment."[178] However, in retrospect this is an over-interpretation of the data in this small study based on an exposure that is not representative of fire smoke in general. The study could not rule out a contribution to cumulative damage and risk of accelerated loss of function over time. Indeed, those are the chief concerns today.

This left the field in some turmoil. It seemed obvious that firefighters should be at risk for lung disease, both malignant and non-malignant. However the empirical evidence was not supporting these conjectures. In the end, it was the wrong type of evidence.

Acute Effects

The lung is a structurally simple but vulnerable organ, intimately linked physiologically as well as physically to the heart and circulation, and continuous with the upper respiratory tract, which is the site of many important host defenses that protect it, which shares many responses with the lower respiratory tract (such as airways reactivity) and the digestive system, to which it is related embryologically. Because of its structure simplicity and functional limitations, the lung has only a limited number of possible responses to toxic injury and the immune or

inflammatory reaction to that injury, which can be categorized in general terms as airways responses (reactivity and inflammation), alveolar and vascular responses (pulmonary edema and pneumonia-like inflammatory infiltrate), interstitial responses (most obviously pneumoconioses, of which asbestosis is most commonly cited by firefighters as a risk. (Although asbestosis itself is not observed, the risk of asbestos exposure relevant to cancer has now been indirectly confirmed by the demonstration of high rates of mesothelioma (an asbestos-associated disease) among firefighters[47].) Studies of the prevalence (usually) or incidence of lung disease, symptoms, and loss of pulmonary function among firefighters are relatively few and in the early years mostly cross-sectional rather than longitudinal. The latter is much more useful, both in determining both causation and disease risk and because decrement in lung function over time has high predictive value for individual prognosis as well as group risk.

Studies of lung disorders or of lung function are well-recognized to be subject to bias, most obviously confounding from smoking. Smoking rates appear to be less among firefighters than in the general population, so that there is a built-in over-correction in mortality studies where there reference is the general population but when firefighters are studied alone or with a highly-selected comparison group (such as police), attribution becomes difficult. Survivor bias is a major problem in firefighters, because the well-known "healthy-worker effect" appears to be much less strong, historically, for firefighters than for other occupations of comparable socio-economic status (SES) but has also improved in recent years, creating a temporal discontinuity. (There is also a temporal variation in exposures due to changes in composition of housing and building materials.) Misclassification bias becomes a serious problem in studies of firefighters when attempting to make associations with particular disease categories, such as isolating risk among airways disorders (asthma, bronchitis and bronchiolitis, emphysema and their combinations, in the form of COPD).

Further, knowledge of the respiratory outcomes associated with firefighting has changed in recent years due to intensive studies of the New York Fire Department (FDNY) members who responded to the World Trade Center (WTC) tragedy in 2001, and for which anomalous types of airways disease have been reported (in particular, forms of bronchiolitis previously under-appreciated). These findings support the impression that WTC responders are experiencing different health care outcomes from other municipal firefighters without WTC-related exposures.

Acute Effects on Lung Function

That firefighters may experience short-term drops in blood oxygen (hypoxemia) following smoke exposure has been known for many years and was quantified in the early studies of firefighters at a time when synthetic materials were already installed in residences and office buildings. (Genovese 1977)

In the pioneering Boston studies, acute inhalation to fire smoke in a relatively unremarkable series of fires was noted to be associated with decreases in FEV_1% of 0.050 l on average, a reduction that is significant for a pre-/post-exposure change but not likely to be noticed by the firefighter, and 0.10 l in 30% of subjects suggesting a subset with increased susceptibility (although only one subject in 39 gave a history of asthma). The loss of pulmonary function was transient but was proportional to intensity of exposure. Of interest is that second exposures within hours resulted in greater acute reductions in flow, proportional to the previous exposure. Cough and eye irritation were frequent but not severe.[179] Not commented on was the observation that in a small fraction of observations (roughly a third), flow not only did not decline but increased, greatly so in a few subjects, suggesting some unrecognized mechanism of bronchodilation.

The susceptibility of a subset of firefighters was further underlined with a small case series of prolonged reactive airways disease following exposure to fire smoke containing pyrolysis products of polyvinyl chloride (PVC), which consist principally of vinyl chloride and hydrochloric acid.[180] These cases, two of which would today be considered irritant-induced asthma and the other a severe organizing bronchitis modified by steroids, were used by the authors to highlight the dangers of PVC pyrolysis and combustion products. However, it can also be interpreted as highlighting the paradox that whether from exposure or susceptibility, relatively few firefighters show such dramatic changes.

Firefighters are not immune to the effects of cigarette smoking and evaluation of baseline function must therefore take smoking into account. Comparing smokers and non-smokers, most smoking firefighters had preserved the major ventilator measures of pulmonary function (FVC, FEV_1) although they tended to have symptoms of productive cough, but a minority showed decreased FEV_1, FEV_1% (≤ 70), or dV_{max}, while nonsmoking firefighters did not.) Such results are entirely to be expected among smoking populations.) More interesting, while as expected

small airways disease (by the He dilution method) was present in firefighters in 35% of smoking firefighters, without restriction by age, small airways disease was also present in 13% of nonsmoking firefighters, but only among the nonsmoking firefighters with ≥ 25 years of fire service. The degree of small airways disease was not enough to cause respiratory impairment to be clinically significant. A small subset of these firefighters were engaged in one particular fire but did not show marked changes in their baseline lung function after the fire. The authors commented that their results were relatively benign in part because the fire was not especially severe, as indicated by relatively low carboxyhemoglobin measurements. Even so one of their cases, who had exhausted his SCBA air supply while in the basement of a building and had to breathe smoke required hospitalization and had a profound chronic respiratory impairment and had to leave the fire service.[181] This relatively early study established that smoking played a role in respiratory impairment equal to or more likely greater than fire smoke inhalation under normal firefighting operations, but that under abnormal conditions acute and severe respiratory effects were possible, even in fires that did not involve exceptionally toxic inhalation (such as the combustion and pyrolysis products of polyvinyl chlorine mentioned above).

The issue of susceptibility naturally arises first in the context of airways reactivity and prior history of asthma. Therefore it was natural, in the subsequent ground-breaking experiment, to evaluate the acute response to fire smoke among firefighters in light of their baseline airways responsiveness to methacholine, the provocative test for airways reactivity. In a series of determinations following otherwise unremarkable fires, it was found that 24% of firefighter subjects transiently lost more than 2 standard deviations in FEV_1, although as much as 10% in only two (about 7%) of cases, both of which showed increased methacholine responsiveness. Contrary to expectations, however, the degree of loss was not proportional to the initial degree of airways reactivity.[182] This led the authors to conclude that fire smoke acted by means other and in addition to simple airways irritation. However, three of the five subjects with greatest pre-/post-fire changes in flow had histories of childhood asthma. The study did not factor in smoking history, in part because the design of the study was grounded on physiological rather than toxicological principles and did not take into account possible tolerance effects. It was also impractical, given the study design requiring multiple measures, to recruit a reference population. Unfortunately, the study could not be repeated with a larger population and with a reference group.

[redacted]

Understanding of the acute effects of smoke inhalation has required studies conducted under controlled circumstances. The previous approach of studying firefighters following uncontrolled events proved to be misleading (see above). In practice, this has meant studying lung function, inflammatory responses, and physiological responses following controlled burns or in smoke chambers. In one such study using smoke chambers, in Singapore, an ethnically homogeneous group of firefighters (Malay) without airways reactivity (by histamine challenge) at baseline showed transient, acquired airways reactivity following smoke exposure, and a subset that had prolonged duration of reactivity showed persistence of flow reductions even after reactivity came back to normal after 24 hours.

Similarly, a panel of Seattle firefighters, none of whom had documented asthma, showed exposure duration-related acutely decreased airflows (FEV_1, $FEF_{25-75\%}$) and airway responsiveness to methacholine from their baseline within hours after firefighting, with associated reduction in specific airway conductance. The findings were unrelated to smoking.[183]

Less physiologically-grounded, more clinically-relevant studies also demonstrated that although most firefighters show a relatively small reduction in lung function, principally in FEV_1 and $FEV_{25-75\%}$ (indicative of small airways abnormality), a small subset showed more profound changes that could interfere with function.[184] These changes were independent of lung function.

Further studies during the overhaul phase of firefighting identified it as associated with acute decline in ventilator measures and increased measures of inflammation (CC16 and SP-A, described in the next subsection), and correlated with carboxyhemoglobin levels.[185] This strengthened the growing impression that overhaul involved significant exposure and could be as risk as knockdown. However, at the same time, an anomaly was identified in that similar changes were seen in firefighters who used cartridge (air-filtering) respirators, suggesting that the cartridges were not completely effective protection. This evidence argued strongly for using SCBA during overhaul, rather than relying on air-filtering devices.

Acute onset of respiratory symptoms, including shortness of breath, mucosal irritation and sinusitis were also documented, in addition to transient lung function changes. [186]

At the same time, a parallel series of studies was demonstrating that the same effect was observed among wildland firefighters. (Not reviewed here.) This was important in establishing that synthetic materials were not the only cause of acute lung function change, as wildfire smoke is predominantly of lignocelluloses origin and less irrigating than smoke from burning synthetic

materials. It was unclear which combustion products were responsible. However the wildland firefighter population also demonstrated an anomaly: there were not showing the expected response to increased concentrations of smoke-derived irritants.[187] Rather they were behaving as if exposure to wood fire smoke triggered a limited, maximum reaction.

Acute Inflammation

Concomitant with the changes in pulmonary function are changes in the expression and release of various acute response and inflammatory markers following exposure to fire smoke, in studies unconfounded by smoking. Not surprisingly, exposure to fire smoke provokes an acute inflammatory response in the lung, release of neutrophils and accumulation in sputum, and release within a few hours of biomarkers such as IL-6, IL-8 and TNF-α, accompanied by a rapid decline in IL-10 (cytokines).[188,189] Similar effects were seen in wildland firefighters.[190] The lung response evolves to lymphocyte proliferation and elevation of fibronectin in lavage fluid.[191] (Novel biomarkers, including chitotriosidase, have been studied as a predictor of chronic effects in the World Trade Center population[192] but not as yet among firefighters in general.) None of this is surprising or out of keeping with what is known of the inflammatory response in the lung.

A more specific indicator that may be of value in structural firefighters is elevation in high-sensitivity C-reactive protein (CRP) levels. The elevation in CRP levels predicts reduced levels of airflow, although longitudinal data have not been conducted to assess causation.[193] In addition to suggesting an inexpensive, readily available clinical marker, the finding is also consistent with the view that acute inflammatory change determines functional capacity and that effects might be cumulative.

Acute oxidant and irritant gas exposure may result in deep lung injury and capillary leak (also known in the terminology of pathology as diffuse alveolar damage), which progresses over time (usually hours) to first interstitial and then alveolar pulmonary edema, which carries a high mortality.[194] Fortunately, this outcome is rare in firefighters, despite the potential. The probable reason is that exposure to common combustion products does not include the one combustion product most likely to do this at significant concentrations: nitrogen dioxides. The oxides of nitrogen can be formed from combustion but require high heat or pressure to produce in quantity. Rather toxic inhalation and pulmonary edema are more likely to occur in hazmat situations,

where the combustion source and substrate producees highly reactive chemical products that are relatively water-insoluble and so penetrate to the deep lung, such as phosgene and paraoxons. These situations are fortunately not common.

Transition from Acute to Chronic Effects

Baseline circulating surfactant-associated protein and Clara cell protein (CC16) levels were lower for firefighters than police, in a cross-sectional study.[195] However, this should be interpreted either as suggesting that in between incidents of exposure there may not be not be such a high level of inflammation in the lungs of firefighters.

It now seems clear that most of the acute effects of fire smoke resulting in lung responses are reversible and correct over a relatively short period, under normal circumstances. However, individual firefighters, perhaps responding to unusually severe exposure and personal susceptibility states, may reach a tipping point in which the acute effect results in subacute or chronic injury of such magnitude that it leads to impairment or prolonged recovery.

Chronic effects

Since 2001, the literature on chronic pulmonary health effects in firefighting has been divided unequally between undifferentiated municipal firefighters and respondents to the World Trade Center (WTC) tragedy. While some lessons from the WTC responders are obviously generalizable, much is not. One example is the progression of apparent restrictive disease in a subset of WTC responders which in fact represent air trapping[196] and is suspected to be associated with constrictive bronchiolitis.[35] This is not a feature of the literature on firefighters in general. As noted earlier in this report, the exposure regime and the pattern of health outcomes are different for WTC responders and this is reflected in the compensation criteria for surviving FDNY responders, which is handled separately from claims from other firefighters and which has its own presumption criteria. Thus, this section will mention WTC responders only sparingly and where the issue is narrow and clearly relevant to all municipal firefighters.

Pulmonary Function

One of the seminal studies on firefighters is significant not because it proved an effect but because it provided the explanation as to why other studies did not.

The pioneering studies on lung function among firefighters were conducted in Boston in the 1970's.[179,197-202] Measurement of lung function by spirometry at baseline was repeated at one year and subsequently an average interval of three and one-half years. The study revealed that lung function declined over time but not in a steady way and that the decline was not associated with the frequency of fires attended or, oddly, with smoking history. However, the study had many anomalies. Cigarette consumption was inversely proportional to the number of fires fought. (This is consistent with a firefighter having enough of smoke of any kind, but also introduces a counter-trend that could have confounded the result.) Firefighters who had fought no fires had a higher rate of decline in ventilator measures, both FVC and FEV_1. (This suggests that there was a reason they were being kept away from fires, not that other duties affected their lung function.) Firefighters who had been involved in knockdowns or who had experienced "shellackings" or "pastings" (being overwhelmed by smoke) did not show disproportionate decrements in pulmonary function. However, excluding firefighters on the sick roll or with known illness did not affect the result. A key observation was that 21% of subjects were lost to follow up, a very high number for a longitudinal study spanning only three years, and that those who left the fire service had shown greater than average decrements in lung function on the first round of testing, after one year. Faced with these contradictions, the authors concluded that there were major confounding factors of selection that resulted in affected firefighters being excluded from service.[200] A second study conducted on retirees, showed that selection factors within the fire service resulted in protection of firefighters in that era through transfers, administrative promotions, and especially retirement.[201] A third study at six years showed no accelerated loss of lung function, which was attributed to success in encouraging adherence to SCBA usage. In the six-month study, the authors recognized the earlier pattern of out-migration and internal accommodation within the fire service in their data.[199]

The expected association between firefighting and accelerated decline in lung function was finally demonstrated unequivocally in a cohort of Boston firefighters studied by a different group. They determined that firefighters had a greater loss of pulmonary function than a

reference group followed in a normative aging study, together with larger variation (as measured by standard error, SE) and that the effect was not explained by age alone, initial function, or smoking, although smoking was associated with clinical symptoms (such as cough). For FEV_1, nonsmoking firefighters showed an average annual decline of 81 ± 19 (SE) ml/y compared to 64 ± 3.9 for nonsmoking subjects of the aging study. Initial function was higher for firefighters than for the reference population, which the authors credited to selection bias due to employment standards.[203] This study, by Sparrow et al., served for many years as the cornerstone of our current understanding that exposure to fire smoke is associated with accelerated decline in lung function in firefighters, as it is in other occupations with respiratory hazards.

However, this apparently clear demonstration of an association was then made not so clear by a series of unrelated studies suggesting that cigarette smoking was a clear risk factor for decline in lung function but that firefighting, as a risk factor, showed primarily short-term effects and little evidence for influence in the long-term.[204] [205] [181] However, there were exceptions, two of which demonstrated chronic changes that were associated with respiratory symptoms[184,186] and one which suggested that cigarette smoking, in a population of high-prevalence (43%) smoking Polish firefighters, played a minor role and that the effect of firefighting predominated.

Finally, an important study of professional firefighters in Seattle demonstrated that while ventilatory measures were indeed preserved in a stable population of volunteer subjects (implying the possibility of self-selection bias), the firefighters showed a decline in diffusing capacity ($D_{L\text{-}CO}$) after adjustment for relevant factors such as age and smoking. The decline appeared to have two components: a general trend of decline associated with year and a much smaller decline associated with number of fires fought.[185] $D_{L\text{-}CO}$ has substantial drawbacks as a screening test, so this was not recommended.

Not surprisingly, among premorbid risk factors, firefighters with α_1- antitrypsin deficiency lung function showed accelerated loss of lung function, even in phenotypically PiZ heterozygous firefighters, who have a moderate serum level of circulating protease inhibitor.[206] Although demonstrated for World Trade Center respondents, this particular finding of susceptibility is well accepted and observed in other situations and so is almost certainly generalizable to normal fire smoke and so is mentioned here. Homozygous PiZZ persons are unlikely to qualify or be retained as firefighters because their defect is likely to result in impairment that would disqualify them based on employment standards.

By far the most important susceptibility state across the range of pulmonary outcomes, however, is atopy, the hereditary presdisposition to allergy characterized by asthma, sinusitis, childhood eczema, and allergic rhinitis and marked by an increase in serum immunoglobulin E and accompanied by airways hyperreactivity (the degree of which is quantified by responsiveness to inhaled methacholine). People with atopy are also variably predisposed to other lung conditions which are associated with decline in lung function. (The "Dutch hypothesis", which links this "allergic diathesis" with lung cancer and COPD remains to be proven definitively but is widely accepted.) For firefighting subjects with allergy or asthma, the primary problem is apportioning their decline in lung function among three drivers: atopic predisposition (hereditary), firefighting (acquired and occupational), and smoking (acquired and non-occupational). The problem is complicated in that, as described above, fire smoke can induce airways reactivity acutely. Dutch investigators (no relation) attempted to do so by examining firefighters who had not been exposed to fire smoke for at least 7 days. They found that increased airways responsiveness to methacholine was significantly associated with the number of fires fought in the previous 12 months, after adjustment for smoking (which had an independent effect) and for history of atopy, and that this effect was unaffected by age or gender. There was a strong interaction between atopy and the number of fires fought. The principal conclusion of the study was that firefighters, especially those with atopy, needed to adhere to respiratory protection.[207] However, the major contribution of this study to new knowledge was to elegantly unpack the relative contributions of the three drivers.

Bringing some confusion to the order that had been emerging, a study from South Australia of longitudinal pulmonary function among municipal firefighters.[20] The reference population was a probabilistic sample of the adult (male) population of South Australia, monitored in a longitudinal health survey. The great majority of participants had quit smoking or never were smokers; depending on whether the first or second round of testing was used to define the "cohort", smoking prevalence rates were 5% or 10%. The methodology was somewhat unusual, in that a case definition of accelerated decline in lung function was used to define the outcome (> 50 ml/y, reported to be the average annual decline for heavy smokers in Australia; the average for the general population is about 30); most studies are based on measured airflow or difference from previous measurement, which has many advantages.[208] This study demonstrated that there was more than one trend occurring and probably multiple confounders.

[redacted]

One trend was that younger generations of firefighters showed better pulmonary function at the time of entry into the fire service than their elders, so the population effect overall was clearly confounded by differences in the subcohorts. Another trend was that lung function did decline over time at an accelerated rate in older firefighters (> 45 y), but stayed the same or even increased in younger firefighters (a highly improbable result); the control population showed the expected slow longitudinal decline. The third trend was that preservation of lung function was associated with active use of respiratory protection. Firefighters gained more weight (although this finding was not statistically significant) than reference subjects. They did not report more asthma but did report a lower prevalence of chronic bronchitis and emphysema (6%) compared to reference subjects (27%), as would be expected among nonsmokers. Yet another trend, acknowledged by the authors, is the healthy worker effect.[20]

This study has many issues, which the authors recognize. One is that the follow-up time was very short, less than 3 years on average, possibly too short to establish a stable trend against a background of some variability. There were probably too few smokers to study interactions with smoking. Because of this, the proper comparison might have been between firefighters and nonsmokers in the reference group, which appears not to have been done, although it should have been taken into account in the regression model. On the face of it, the finding of a greater trend toward loss of lung function among firefighters who do not reliably use respiratory protection, which suggests that fire smoke has an effect, is inconsistent with no loss or an increase in lung function among firefighters compared to non-firefighters. Of course, an actual increase in lung capacity is not strictly possible, in the absence of disproportionate reversible airways disease, in other words, asthma prevalent in a very large percentage, which was ruled out in any case. It may be that the case definition approach turned a continuous function (airflow) into a binary or step function and so distorted the regression analysis. There was a difference in the methodology of spirometry, with stricter protocol for the firefighters, but a systematic error would not explain why firefighters' lung function appeared to increase. One possibility is that if there was significant error in the measurement, in which case there may have been a statistical regression to the mean after the initial measurement gave a skewed response. In short, this study is essentially uninterpretable on the basis of longitudinal trends, probably because of multiple confounding and dissimilarity in smoking prevalence, although it is suggestive that respiratory

protection is a successful means of preserving lung function. As follow-up lengthens, the meaning of these trends may become clearer.

What is required, clearly, is a longitudinal study of firefighters without exceptional exposures large enough to have sufficient power to resolve trends due to occupation, smoking, atopic diathesis (including asthma history), and aging. Such as study is currently underway in the FDNY, where established protocols and identical equipment and technical staff ensured consistency. The FDNY team is following 940 new firefighter hires since the WTC tragedy, and using a much smaller number (97) of EMT personnel as a reference group; firefighters have more stringent employment standards. The prevalence of smoking overall was 3.5%. Data from the first five years has now just become available, separated by overall rates and those for non-smokers. The firefighters were significantly taller and had higher initial ventilator function; turnover was very low and the few firefighters who separated were individually documented not to have left for respiratory disability. Perhaps surprisingly, the study demonstrated an average loss of ventilator function as FEV_1 of 45 ml/y for both groups, with essentially no difference (there was slightly greater decline in FEV_1%, which is a calculated rather than a primary indicator). There was no difference observed between nonsmoking and smoking firefighters, probably because the period of follow-up was too short for this to become apparent in the relatively young population of new firefighters; weight gain was the only factor observed to affect the trend in both occupational groups. The authors pointed out that in addition to being much larger than previous studies and having a much lower smoking prevalence to contend with, this was the first study to document longitudinal trends in a firefighter population with mandated and high levels of SCBA compliance.[21]

Thus, the most defensible conclusion at present is that the current generation of firefighters is not demonstrating accelerated decline in ventilator function, at least at this early time in their careers, probably because of enforced adherence to policies requiring use of respiratory protection. Older cohorts, however, may demonstrate some accelerated loss of airflow but the situation is complicated by cohort effects and is highly multifactorial, with ample room for confounding. Taking into account the important role of SCBA as effective protection, it can finally be concluded that fire smoke is indeed associated with accelerated decline in ventilator function but that the contemporary firefighting profession is protected to the extent that firefighters adhere to appropriate respiratory protection.

[redacted]

Clinical Outcomes

Pulmonary function reflects physiological changes. Clinical outcomes involve the appearance of distinct symptoms (which in lung disease emphasize on cough, shortness of breath, and wheezing) or the diagnosis of specific diseases. The two main diagnoses of concern are asthma and obstructive airways disease, not to be confused with COPD (which implies the characteristic lung disorder due to smoking). Bronchitis, as has been shown, clearly occurs as an acute response and a chronic form of bronchial inflammation (as opposed to the characteristic lung disorder of chronic bronchitis) may contribute to asthma and obstructive airways disease in firefighting. Interstitial disease due to pneumoconiosis does not seem to occur in firefighters, although exposure to asbestos is confirmed and some mineral dust exposure may occur incidentally in the course of duties. (Mineral dust exposure is much more likely to be a factor in the WTC responders.) Sarcoidosis is discussed elsewhere in this report, as is lung cancer.

Asthma

By definition, asthma is a disorder of reversible airways obstruction. Because it is defined by a nonspecific functional change and not by pathology or etiology, asthma is not really a single disease, although the respiratory disorder that children get and often outgrow probably is a coherent diagnosis. There are many other types of asthma but two are of most concern to firefighters. One is the importance of a history of asthma, either current or in childhood, as a marker for atopy and reactive airways, which may render a firefighter more susceptible to the effects of fire smoke. The other is irritant-induced asthma, which is a form of new-onset asthma in the adult that occurs when inflammation is induced in the airway by exposure to chemical irritants, as occur in abundance in fire smoke. It is suggested (see earlier in this report) but not proven that fire smoke is probably more irritating than cigarette smoke because the latter contains some agents that tend to damp down inflammation, including nicotine. This means that for a given exposure, fire smoke is likely to induce more inflammation acutely and ultimately induce greater chronic effects than the same exposure to cigarette smoke. Of course, exposure to cigarette smoke is usually much higher because it is inhaled intentionally and repetitively into

the respiratory tract as a nicotine-delivery device. Fire smoke is likely to cause chronic irritant-induced occupational asthma, whereas cigarette smoke induces its characteristic deep lung lesions resulting in emphysema in part because the smoke is more tolerable in the short term.

Given the acute changes in airflow and the known susceptibility of the airway to irritant-induced inflammation and bronchospasm, it is rational to expect that asthma rates would be elevated in firefighters. Surveillance data, which inevitably are biased by gross underreporting, suggest that firefighters had the second-highest reported rates of work-related asthma among all occupations in California, after janitors, in the mid-1990s.[209] Because of extreme and often systematic biases in reporting, which amplify the effects of small errors and distortions, reported rates are untrustworthy and the remainder of the list (which included bus drivers and "eligibility clerks" among high-risk occupations) is not so plausible.

Prevalence studies of asthma among firefighters, using a battery of diagnostic techniques with bronchoprovocation being the gold standard, confirms that asthma is under-diagnosed by community physicians among firefighters, at about 6% for Swiss firefighters; a prevalence of 14% was suggested as closer to the true value.[210] Brazilian municipal firefighters had a prevalence of symptoms leading to clinical diagnosis of asthma (without the gold standard) that was about 9.3% and higher than police.[211] It would appear, then, that Swiss physicians are relatively conservative in making the diagnosis. However, these prevalence rates of asthma are still not far from reported asthma prevalence in most developed countries.

It should be noted that the default diagnosis of many uncritical clinicians for any variable lung disease is often "asthma", especially in a non-smoker. (In a smoker, it would be "COPD".) Some of the WTC responders have carried the diagnosis of asthma from their local physicians without confirmation or specialist evaluation. They are now being reevaluated through the efforts of monitoring programs, often receiving more nuanced diagnoses.

In short, given the combination or accelerated decline in ventilator function (see earlier discussion in this section) and induction or irritant airways inflammation, some individual firefighters may be pushed into respiratory impairment or insufficiency, particularly following poor recovery from unusually intense exposure situations. Thus, reversible airways obstruction in a form of irritant-induced asthma cannot be ruled out for firefighters but it must be very uncommon, especially with adequate respiratory protection. The picture is undoubtedly confused by inconsistency in the diagnosis of asthma.

[redacted]

Chronic Obstructive Airways Disease

Chronic obstructive airways disease is used here as a descriptive term for acquired fixed airflow obstruction with or without airways reactivity, in order to emphasize the functional changes and to avoid term “COPD”. “COPD” is sometimes used casually in medicine and epidemiology as a generic term for fixed airways obstruction, but in occupational and pulmonary medicine it has a well-understood and accepted definition as the name of a particular disease associated with smoking.

Chronic obstructive pulmonary disease (COPD) is a clinical entity, associated with a smoking habit, that involves individually variable contributions of three specific processes. 1) Emphysema is a general term for simplification (destruction) of the lung architecture. In smoking-related emphysema, it starts at the level of alveoli and shows a specific pathology (peribronchiolar alveolitis). As it progresses, it results in fixed airways obstruction and a rapid decline in ventilator function over the long term. 2) Chronic bronchitis, an inflammation of the airway wall, can be a primary diagnosis but is most often minor or absent in COPD. 3) Variable degrees of reversible airways obstruction and hyperreactivity, which may or may not present clinically as asthma but is mostly responsible for short-term changes in lung function and is responsive to the same treatment. COPD may have all three elements or proportions of each, with fixed airways obstruction predominating but reversible airflow obstruction being the major target of treatment. There are other emphysemas, asthmas, and bronchitides besides those associated with smoking. They are not “COPD” in the true sense.

The population mortality studies discussed earlier (in great detail for cancer outcomes) are consistent in not showing elevated mortality from what would be recorded (and routinely misclassified) on a death certificate and compiled in vital statistics as “COPD”, asthma, or total respiratory disease. Much as in asthma among firefighters, the search for the crime in the form of chronic obstructive airways disease associated with firefighting has not turned up either a victim or a smoking gun.

Firefighters can develop COPD if they smoke. However, fixed airways obstruction among firefighters, in the absence of smoking, would not be true COPD. It would be a form of chronic obstructive airways disease with its own features, characterized by accelerated decline in

ventilator function (see above). It would lack or modify the characteristic pathology of peribronchiolar inflammation and would probably have more regular features of bronchitis, with changes in the airway epithelium characteristic of chronic inflammation. To date, evidence for a novel type of chronic airways obstruction has been difficult to find. Even at the accelerated loss of function documented in older firefighters, they may escape respiratory impairment in their lifetime if their smoking habit is not extreme.

One reason for this paradox is that firefighters are under so much selection pressure. Individuals with a susceptibility to lung disease, either known or inapparent (see the reference above to the "Dutch hypothesis") may be self-selected to be more resistant to the irritating effects of fire smoke. This is speculation, because there is no biological marker for the effect other than rate of decline in lung function over time.

Individual cases of emphysema, respiratory disability, and respiratory failure are documented, such as the PVC-related cases noted above. Unfortunately, the few older case reports lack essential exposure information and clinic-pathological correlation and have been silent on degree of airway inflammation and presence or absence of obliterative bronchiolitis. These features would be considered essential to a contemporary case report. There have also been clear cases of misdiagnosis and misclassification in the literature, including asthma that was demonstrated without question to be advanced emphysema but was still misidentified as asthma in the title of the article.[212]

In short, given the probability that accelerated decline in ventilator function (see earlier discussion in this section) could push some individuals into respiratory insufficiency, particularly following unusually intense exposure situations, fixed airways obstruction and chronic obstructive airways disease cannot be ruled out for firefighters but it must be rare.

Conclusion

The weight of evidence at present supports the conclusion that individual firefighters may be at risk for disabling lung disease following specific, acute events associated with extreme exposure, which may interact with individual susceptibility. Individuals who have experienced these catastrophic events will have a compatible history.

The weight of evidence at present supports the conclusion that firefighters are at general risk for lung symptoms and decline in function in a form, probably highly variable, that is typically diagnosed as asthma. The condition is more complicated than conventional intrinsic asthma and is not well characterized. It may clinically resemble adult-onset, intrinsic asthma (which is actually often a form of chronic bronchitis) but in fact may consist of the inexorable accelerated decline of pulmonary function into clinical impairment, combined with a superimposed irritant-induced bronchitis. The clinical picture in firefighters is confused in part because of intense selection pressure frequently resulting in high or supranormal lung function on entry and preservation of lung function over many years despite inhalation of irritants that would normally be associated with accelerated decline. The picture that results appears to feature unusually stable lung function at baseline on which is superimposed multiple episodes of short-term, acute changes from which the lung recovers easily, until an exceptional exposure reaches a tipping point.

The weight of evidence at present does not support the conclusion that firefighters in general are at risk for chronic fixed obstructive airways disease as a direct result of firefighting in unexceptional situations. It is well known that unusually intense and toxic exposures (for example, to oxidant gases) may induce different types of obstructive airways disorders (such as bronchiolitis obliterans) but such cases are fortunately unusual and demonstrate comparible histories. Firefighters are not immune to smoking-related COPD if they smoke. Older firefighters who smoke and who have documented histories of participation in many knockdowns might experience an accelerated decline in lung function that "catches up with them" during their lifetime and presents as the onset of "COPD" after retirement, since clinicians would not be able to distinguish COPD from other forms of fixed airflow obstruction. Across the board, however, fixed airways obstruction does not appear to be a general or common problem among firefighters, contrary to expectation. This conclusion cannot be held too dogmatically, however, because all studies necessary to resolve the complicated issues have not been done.

NEUROLOGICAL AND SENSORY DISORDERS

Very broadly, neurological disorders can be distinguished as diseases intrinsic to the nervous system and those secondary to the nervous system that arise for vascular insufficiency, which, with one exception, are much more common. That exception is noise-induced hearing loss (NIHL), a sensorineural disorder that is among the most common occupational diseases.

Mortality data is the usual way to evaluate other neurological disorders, and that means that the frequent conditions in cohort studies are dominated by stroke, the risk for which happens to be reduced among firefighters. Unless developed for a specific study in the community, neurological disorders are not entered into registries and, with the exception of NIHL, are not tracked for surveillance purposes with incidence data.

Intrinsic neurological conditions, such as degenerative neurological diseases of the brain, spinal cord, autonomic nervous system, or neuromuscular junction are much less common than stroke, which is caused by disorders of the blood vessels and clotting mechanism. Most degenerative neurological diseases occur relatively early in life, except for Alzheimer's diseases and other forms of dementia, which mostly occur after retirement and are usually not direct causes of death.

The rigorous selection and retention bias for fitness among firefighters ensures a strong healthy worker effect, in that firefighters who show early signs of neurological or neuromuscular disease (such as loss of strength, loss of coordination, seizures, cognitive disorders) are unlikely to be hired and unlikely to stay on the job once the symptoms present themselves. It is therefore not surprising that neurological disease is an uncommon cause of death among firefighters and so rates are lower among firefighters than in the reference populations.

Among the extant occupational cohort studies of firefighters, most show very low mortality from neurological diseases. Most of the firefighter cohort studies, especially the older and smaller ones, do not even report neurological diseases as a separate category. Among those that do[12,18], the risk ratio is at or close to about 0.75, although most of these studies have wide confidence intervals due to the small number of cases, ranging down to 0.56 (Tornling) and a statistically significant 0.47 (0.27 – 0.83)[11].

Stroke (Cerebrovascular Disease)

The literature on firefighting and neurological disorders is limited. The risk factors for the most common neurovascular condition, stroke, are generally the same as for heart disease. Stroke risk factors are also discussed under cardiovascular disorders.

Thus, it is not surprising that rates of stroke as a cause of death closely parallel death from ischemic heart disease (mostly myocardial infarction, the principal form of heart attack). Both stroke and ischemic heart disease mortality is decreasing, largely due to better treatment, but deaths from both are frequent and improvements in survival are observed across the population, not just in fit populations such as firefighters. Therefore, mortality compared to the general population remains a reasonable measure of stroke risk among firefighters and by that measure many studies of sufficient power show a significant and sometimes pronounced deficit of deaths from stroke among firefighters. For example, Baris et al. shows a relative risk of 0.83 (0.69 – 0.99).[11] This deficit in stroke mortality has been present for a long time. Vena et al. showed a risk (PMR) of 0.76, compared to police.[160] However, this is a reflection of underlying cardiovascular risk factors, which tend to be favorable in modern firefighters. Thus the explanation for the favorable experience with stroke among firefighters needs to be addressed together with other cardiovascular risk factors, not with intrinsic neurological conditions.

Motor Neuron Disease

Motor neuron disease is a general rubric for a collection of relatively rare disorders, of which the most common is amyotrophic lateral sclerosis (ALS), a progressive disease that occurs in adulthood, preserves cognitive function and awareness, and typically results in a relentlessly advancing weakness until the muscles of swallowing and respiration no longer function, at which point the disease is always fatal due to pneumonia or respiratory failure.

Using mortality data (which is only reliable for some neurological disorders) derived from the National Occupational Mortality Surveillance System from 1982 to 1991, NIOSH investigators found an excess of deaths (PMR% 318, no confidence interval reported, with 6 deaths; population of firefighters not reported) for firefighters from motor neuron disease, but not other neurodegenerative disorders. However, no further information is available and, oddly,

firefighters are not listed in an accompanying table of highest-ranked occupations at risk of motor neuron disease by race and sex, although athletes, with similar characteristics and a lower risk, were entered. This study design is usually considered insensitive, demonstrated an excess of death from motor neuron disease for firefighters, along with other occupations, but in this case the study overcame many of its intrinsic statistical limitations by compiling large numbers. There were many occupations with higher and more stable risk estimates, including veterinarians, several of which had astronomical risk estimates based on small numbers. The study suggested that neurodegenerative disorders, in general, might have a link to solvent exposure (some solvent chemicals also being present in fire smoke) but sedentary and knowledge workers also showed elevations.[213]

The study was repeated by NIOSH approximately ten years later on mortality data from 1992 to 1998 using the same general methods, by the same group. However, firefighters were inexplicably omitted, although the patterns for solvent-exposed workers and knowledge worker remained.[214] Thus, the later study cannot be taken as a replication, since it appears that, for whatever reason, public safety workers were not studied.

However, a contemporary study of occupational associations of AML in Italy has shown a doubling of risk for firefighters (OR 2.0; 1.2 – 3.2).[215] The study was conducted not to identify a toxic exposure but to test the authors' hypothesis that tissue hypoxia is a risk factor. The authors hypothesized that ALS may occur in response to hypoxia in individuals with a genetic susceptibility.

Given that the first study was relatively weak and showed a finding that could be explained by chance alone due to multiple comparisons, the epidemiological evidence for an association between firefighting and motor neuron disease may be considered unpersuasive at this time. On the other hand, two studies have found an association with firefighting at a risk estimate that is not only significant (in one and probably the other) but sufficiently high (≥ 2) to suggest a presumption in the individual case, which is a higher standard than association alone. This cannot be ignored and so in the absence of evidence to the contrary or a reason to believe that there was substantial confounding, the empirical result has to be accepted as the weight of evidence.

There have been numerous other attempts to identify occupational associations with motor neuron disease. Most have suggested an association with rural life and possibly farming,

solvents (including hexane, although this may just be a surrogate exposure), pesticides, electrical shocks and exposure to strong electromagnetic fields. Recent studies have focused on cigarette smoking and formaldehyde exposure, which could be consistent with a risk for exposure to combustion products but is not strongly suggestive.

Neurosensory Disorders

The common neurosensory disorder of firefighters, as with most occupations, is noise-induced hearing loss (NIHL).

Firefighters are screened on hire for good vision. Visual impairment occurring due to occupational risk factors is not addressed in the literature but since this is monitored with regular physical examinations, the omission probably reflects lack of a problem rather than oversight.

Hearing

For many years, the literature did not reflect the true dimensions of the problem of NIHL among firefighters. NIHL is primary a disorder of cumulative or repetitive trauma to the auditory hair cells in the cochlea, the organ of hearing. Individual hair cells are "tuned" to particular frequencies. Loud noise damages the hair cells tuned to the corresponding frequency. Certain frequencies, particularly at and around 4000 Hz (a Hertz is a "cycle per second") are important in comprehending speech but are particularly vulnerable both biologically and physically because of the sound frequencies commonly encountered in the workplace. In some cases, NIHL is a mixed conditions because it is also associated with atherosclerosis and smoking (probably because of vascular disease affecting the blood supply to the inner ear) and solvent exposure, which is related to direct neurotoxicity of the ciliated hearing cells. However, the necessary hazard that must be present for NIHL to occur is loud noise.

Noise exposure is a common and recognized hazard in firefighting, but the literature on noise-induced hearing loss is scanty, largely obsolete, and rudimentary. Contemporary equipment is much less noisy than in the past but there few recent noise surveys have been published for the fire service. Major sources of noise include vehicles while in transit with the

warning siren blaring and water exiting the hose at high pressure. Because of communication and warning requirements and the adverse conditions of hot and often steamy conditions, it is not generally feasible to wear hearing protection while actively engaged in firefighting, although it may be possible while in transit.

Exposures to noise levels in excess of 100 dBA (an uncomfortably high level of noise) for very short periods may occur while in transit with the siren on, yet these levels may still conform to both the "ceiling" (peak) and the the 8-hour time-weighted average occupational exposure limits (the national occupational noise standard in Australia is 85 dBA 8-hour averaged daily exposure with a 140 dBC permissible peak level).[216]

Sound levels within fire trucks, which may reach 110 dBA, have long been said to comply with American occupational health regulations and hearing thresholds for firefighters have been reported to be comparable to workers not exposed to noise within the cabin of fire trucks.[217] However, this is misleading. The US OSHA noise standard is a time-weighted average and compliance with the standard was a function of short duration. Peak noise levels may be an independent risk factor for NIHL and certainly is when it begins to approach impulse noise levels. The OSHA PEL for noise is also well known to be inadequate in providing protection, in that it is not fully protective against hearing loss, even for ears that do not have a biological susceptibility or preexisting disease.

It has also been suggested that firefighters are not at risk for NIHL and show no decrement consistent with occupational loss of hearing on serial audiometry.[217,218] Further, studies that showed lower noise exposure, except during emergency response still demonstrate that a substantial fraction of firefighters had NIHL.[219] This literature left the impression that NIHL among firefighters was not likely to be work-related. This conclusion no longer stands.

More definitive recent studies demonstrate clearly that currently a high percentage of municipal firefighters (40% in San Francisco in the 1990's) do have NIHL, that the frequency and severity is associated with duration of service as a firefighter, occurs more frequently in the left ear, may occur early in the career of a firefighter, and that hearing protection was effective but only used by 34% of firefighters.[220-222] The loss of hearing follows a trend of accelerated loss over age that is particularly pronounced in cases in which there has already been significant loss. This means that damaged ears are more susceptible to further damage.[223]

Hearing conservation programs for firefighters are not universal but when voluntary programs have been introduced compliance has appeared to be good with support and incentives.[224-227] On the other hand, outcome data are not available from current demonstration programs.

On the face of it, noise-induced hearing loss is an occupational risk of firefighting and one that can be mitigated with prevention of unnecessary exposure to noise. Noise-induced hearing loss is reported to be more frequent at earlier ages among firefighters than in the general population and to be more common in the left ear, which in North America is the ear facing the window on the driver's side.[228]

BEHAVIOURAL DISORDERS

Psychiatry makes distinctions among behavioural disorders, distinguishing between psychoses, neuroses, serious personality disorders, emotional disturbances, developmental disorders, and mental retardation. None of these are relevant to the compensation in the fire service, because when they are disabling they preclude hiring or retention as a firefighter. Milder personality types (as opposed to disorders) may play a role in adjustment to occupational stress but as a contributing factor, not as an effect. Of greater concern with respect to disability and compensation are adjustment issues, addictions, posttraumatic stress disorder 163and reactive depression.

The literature on psychiatric morbidity among firefighters clusters around four distinct issues:

1. The prevalence of mental illness among firefighters, with particular reference to depression
2. Suicide risk
3. Alcoholism
4. Post-traumatic stress disorder and related indicators.

No surveys were found of the prevalence of mental illness among firefighters, although the literature seems to anticipate high levels of depression and adjustment disorder. This is implicitly assumed to reflect high levels of stress and exposure to unsettling events.

Firefighters clearly share the risk of mental illness with the general population but there may be factors operating that modify its prevalence and presentation. The fitness standards, preplacement evaluation procedures (post-hire, pre-assignment, as required by the Americans with Disabilities Act), and retention patterns of the fire service, which values team effort, reduce the opportunity for persons with severe mental health or personality disorders to make a career in the field. Firefighters typically have high levels of community support and camaraderie, which are important for resilience and the ability to cope with stressful events. As pubic employees, they also have access to relatively high-quality support services, such as employee assistance programs and medical interventions.

Suicide Risk

Mortality from mental disorders is generally associated with suicide, usually in response to depression. Suicide is often concealed by misclassification on death certificates, making it difficult to identify. Thus, the contradictions and interpretation issues for cohort mortality studies are considered in the next subsection.

In general, extant studies document a low rate of suicide for firefighters, taken at face value. New Jersey firefighters showed a low rate of 0.70 (PMR).[76] Many studies, for example a major study in San Francisco, did not examine suicide as a cause of death.[18] Buffalo firefighters (1987) showed the lowest reported rate, at 0.21 (statistically significant).[160] Sweden (Stockholm, 1994) was not far behind, significantly reduced at 0.33.[90] Washington state firefighters showed a low risk at 0.37[145] and nearby in Alberta, municipal firefighters showed an exceptionally low rate of (SMR) 0.39 (not statistically significant, because it was based on only seven cases)[12]. The recently published NIOSH study, on the other hand, reported risk estimates of 0.87, with variation among the three cities among which San Francisco had the highest rate, at 1.24 (not significant), which was the highest reported for any fire service.[47] These data may be interpreted as suggesting that firefighting has a strong protective effect against suicide.

However, there may be more to the story. In Alberta, the rate for suicide was low but death attributed to mental disorders (which usually occurs by suicide) was highly significantly elevated at 4.14.[12] This suggests possible misclassification, perhaps intentional as a euphemism.

Combining the two causes of death and recalculating the risk estimate yields a risk estimate of 1.16, a modest and not significant elevation.

The NIOSH study showed rates of death from mental disorders that were near unity, meaning that they were similar to the reference population,[47] which begs the question of why this cause of death did not show a strong healthy worker effect, as would be expected.

Thus it is not certain that firefighters actually do have rates of suicide far below the general population, as reported. These reports may be deceiving, because suicide as a category of cause of death is notorious for underreporting, especially when the death is certified by physicians with a close relationship to the family or when it occurs in equivocal circumstances such as drug overdoses. These biases might affect firefighting more than the reference population.

At present, there is little to suggest that firefighters on the whole have an elevated risk of suicide, but it is unlikely that their deficit of suicide is as low as reported.

Alcohol Abuse

This is a very sensitive diagnosis, subject to many of the same biases as described above for suicide.

Death by "alcoholism" can take various forms but the most reliable surrogate cause of death is cirrhosis of the liver. As noted under GI disease, cohort mortality studies of firefighters that examine cirrhosis as a cause of death may show unremarkable rates of mortality[11,90,160] but many do show mortality elevated from cirrhosis, up to a significant risk estimate of 2.27 in San Francisco,[18] or hints that even if the overall mortality is not elevated, there is a relationship with increasing age of the firefighter.[76] NIOSH showed an elevation in mortality from cirrhosis of 1.26, consistently elevated across three cities and statistically significant in two of the three as well as overall.[47]

Data on alcohol abuse are not readily available, because firefighters have been aggregated with law enforcement as public safety officers in otherwise important studies.[229] The overall conclusion is that alcohol abuse is not more prevalent in public safety occupations but that the pattern of binge drinking may be more common. Given the different cultures of police

and firefighters, however, and the presumably greater numbers of police in these studies, one cannot assume that this generalization applies to firefighters.

In Taiwanese firefighters, the prevalence of major depression was found to be 5.9% and that of "problem" alcohol use 8.6%. Depression, but not problem alcohol use, was determined to be correlated with effort-reward imbalance and high psychological demand, as predicted by current theory. It is not clear what transcultural generalization these findings have that would apply to Australia or that firefighters of Asian ethnicity would have the same experience in Australia, so extrapolation is not recommended. The value of this study is that it supports the well-established observation that perceived inadequate effort-reward imbalance has an association with mood and that the detrimental effect occurs in the fire service, whatever its secondary and community rewards.[230]

Taken together, the pattern provides moderately strong evidence for the presence of severe alcohol abuse among some firefighters, likely extending into retirement. No generalizations can be made over the entire occupation, however.

Post-traumatic Stress Disorder and Related Conditions

The literature on psychiatric illness and firefighters is large and is dominated by studies of post-traumatic stress syndrome (PTSD). It is not feasible to attempt a comprehensive review. In many cases, firefighters' issues play a secondary role in the studies because firefighters are subjects for broader investigation of PTSD and its risk factors. Procedures for making the diagnosis of PTSD and criteria for adjudicating claims based on this diagnosis are well established, if always controversial, and little additional value is anticipated in reviewing the literature for recommendations. There is also a risk that setting forth a different set of recommendations, with no more validity and less support than those that are currently used, would be detrimental rather than constructive. However leaving it out entirely seems inappropriate, so a few comments will suffice.

Post-traumatic stress disorder (PTSD) is not the only psychiatric response to an overwhelmingly stressful life event. It is not even the most common. There are other ways of responding behaviorally to traumatic events, such as depression and self-medication with alcohol or drugs. Studies of firefighter responders to the horrific place crash in Amsterdam in 1992

showed higher frequencies of reports of multiple symptoms, rather than reporting single or isolated health complaints, and were more likely to attribute their health problems to the incident, without demonstrating the cardinal signs of PTSD.[231,232]

GENITOURINARY SYSTEM

There is no suggestion in the literature for kidney or urinary tract conditions being associated with firefighting, except the cancers, as previously noted. The NIOSH Study did show a significantly elevated risk of death from acute glomerulonephritis (a kidney disease; SMR 1.56; 1.07 – 2.20), for which there is no obvious connection with firefighting, but not for individual cities and not for a long list of other genitourinary conditions.[47] This isolated finding probably represents an anomaly arising from multiple comparisons but deserves watching when other studies provide data down to this level of detail for kidney disease.

REPRODUCTION

There has been concern for some time on the potential reproductive hazards associated with fire smoke and inhaled contaminants, especially for women firefighters.[233,234] There is contradictory and probably insufficient evidence to suggest congenital defects among offspring of firefighters.

Most attention has focused on chemical hazards for both male and female firefighters. As a practical matter, however, the primary focus has been on effects on the male side male because there have been so few female firefighters until recently. For occupation to have an effect on the male side, it must be assumed that there is a genotoxic or epigenetic effect that is hereditable, rather than *in utero* effects. This considerably narrows the range of plausible congenital anomalies.

However, the hazard of greatest theoretical concern for reproduction in female firefighters has actually received scant attention: heat. Hyperthermia is known to be highly fetotoxic and is associated with severe congenital defects in experimental studies. Human beings have the capacity to control core temperature across a wide range of environmental temperatures, so the effects of external heat should be mitigated up to the level of physiological capacity.

However, pregnancy reduces a woman's capacity to maintain stable core temperature, to an unknown and probably variable degree (experimental studies not being possible) and whatever risk there may be would be worse with dehydration. Although 2.1% of fire scene injuries (in 1980) reported to be due to heat exhaustion and some number of those are likely to represent incipient hyperthermia, the risk to the offspring of pregnant firefighters has still not been fully assessed.[234] (Evanoff 1986)

An "exploratory" case-control study in British Columbia found a markedly and highly significantly elevated risk (up to OR 5.9; 1.60 – 21.83, for ventricular and also atrial septal defects compared to the general population) for two types of heart defects in children of firefighters, as compared against the general population and against police.[235] However, this dramatic finding has not been replicated. A case-control study performed on Toronto firefighters between 1979 and 1986 in order to confirm this finding demonstrated a much lower and non-significant odds ratio (1.22; 0.46 – 3.33) for the same categories of congenital anomalies.[165] Similarly, contemporaneous data from a birth outcomes registry in Sweden did not show an effect, either overall or for the specific heart defects reported in the original study.[236]

The finding has carried over into the general literature on birth defects[237] without mention of the negative studies that followed. A comparison with other occupations involving exposure to solvent chemicals, such as painters, shows that the putative risk for the specific congenital defects were not shared, since solvent-exposed workers tended to show spina bifida and patent ductus arteriosus (which is a large vessel defect distinct from congenital cardiac defects) rather than the septal defects reported by Olshan et al.

Likewise, a study based on the congenital defects registry of Atlanta found no excess risk for cardiac defects. On the other hand, firefighters were disproportionately and markedly represented among the fathers of children born with cleft lip and palate (OR 13.3; 4.0 – 44.4, but based on only four cases), heart anomalies (4.7; 1.2 – 17.8, based on three cases) other than ventricular septal defect (0.7; 0.1 – 5.3, based on a single case), clubfoot (2.9; 1.4 – 6.0, 13 cases), and hypospadias (2.6; 1.1 – 6.3, 8 cases), with non-significant elevation for hydrocephalus.[238] However, these particular congenital anomalies do not go together logically and do not fit the timing of the common mechanisms of birth defects. The window of vulnerability for most of them occurs during the first trimester *in utero*, not before conception, and clubfoot and hypospadias are fetal, not an embryonic phenomenon. Thus, the plausible

associations for firefighters will probably require much more study and more robust numbers before it can be assumed that the children of firefighters are at risk.

The absence of replication, combined with the absence of reports from congenital defects registries and other research centres that have a robust interest in associations with congenital heart disease, suggest that the findings for heart defects were at least not generalizable and cannot be considered definitive evidence for a risk for offspring of firefighters, but there are sufficient grounds for concern to monitor birth outcomes more closely and to conduct further studies.

SKIN DISORDERS (NONMALIGNANT)

Obviously firefighters may develop skin diseases like everyone else, and in Australia they are at risk of ultraviolet radiation effects, which are well known. Australia is the world leader in awareness and protection against ultraviolet-induced skin cancer and other effects. Skin cancers, with an emphasis on melanoma, have been discussed earlier in this report.

No references were found specific to dermatitis or skin conditions in firefighters. Except in the case of systemic diseases with cutaneous manifestations, including autoimmune disease with dermal presentations, skin diseases are rare as causes of death. Registries of dermatopathology are common but registries of non-malignant skin diseases are rare and almost never studied for occupational associations.

INFECTIOUS DISEASES

Infectious disease risk for firefighters has centered on blood-borne and respirable pathogens that can be transmitted from patient to first responder.[239] The same risk factors may not apply to military firefighters, given the division of role and responsibilities of medical corps officers in Australia, and field medics and emergency medical technicians elsewhere. This literature will not be reviewed in detail but representative papers will be cited to support the points made.

The diseases of chief concern are hepatitis B, hepatitis C, HIV/AIDS, tuberculosis, and MRSA. These diseases are not prevalent in the Australian Defence Forces due to screening and mandatory disclosure and lack of opportunity for exposure.

Hepatitis B was long considered the single greatest hazard for emergency response personnel. Hepatitis B virus is easily transmitted by multiple routes and is one of the principal targets of universal precautions. There appears to be no evidence for a significant elevation in hepatitis B infection among firefighters up to the last decade.[240] This is not surprising, in that the diseases are much dreaded and effective measures for self-protection are well established. Among civilian firefighters, persons who are positive for hepatitis B generally have at least one non-occupational risk factor, implying that infection is unlikely to arise from work. Occupational risk has probably dropped further since then due to increased adherence to universal precautions. Military personnel are also likely to be a lower risk for hepatitis B infection than the general population, being young, screened, and to some extent supervised.

Hepatitis C infection, similarly, was not elevated among first responders overall but was correlated with needlestick risk, older age, and exposure to high-risk populations[241,242], implying that some cases did arise from occupation but at a low rate. Hepatitis C is more often associated with intravenous drug use than even hepatitis B and is therefore less likely to be prevalent in an active-duty military population.

The HIV/AIDS virus (human immunodeficiency virus, the pathogen responsible for AIDS) is less readily transmissible than hepatitis B and has similar characteristics. The military population is likely to have a low prevalence of HIV/AIDS infection. No papers were found on this particular infection but normally HIV/AIDS infection from occupational exposures (principally needlestick injuries) closely track hepatitis B rates. There is no obvious reason to suspect otherwise for military firefighters, who are presumed to be at low risk.

Australia has a low incidence of tuberculosis, among the lowest in the world, and the disease is primarily confined to specific subgroups, well known to public health authorities, and to immigrants. There is a serious threat within the region of introducing multiple-drug resistant tuberculosis into Australia. However, the proportionate risk at the present time for military firefighters and for other first responders, other than those serving civilian subgroups at risk, must be accounted to be very low.

Methicillin-resistant *Staphylococcus aureas* is any strain of the bacterium resistant to this essential antibiotic. MRSA is spread primarily by direct contact, which occurs more often in hospital settings but occurs as well in the community. MRSA infection is acute and it is unlikely that a compensable illness would result in large numbers or that an individual case would present an adjudication problem.

In summary, infectious diseases, while a potential hazard of firefighters in general, are unlikely in practice to result in compensable illness very often and when they do there are likely to be individual-specific circumstances. Military firefighters are probably at low risk.

MUSCULOSKELETAL DISORDERS

Comparatively little has been written on musculoskeletal disorders associated with firefighting, perhaps because the patterns are not unique to the occupation and compensation issues, while sometimes contentious, are not much different from other employee groups.

There is a methodological issue with the literature on firefighters that is shared with other occupations. To be consistent with current practice, the definition of an "injury" should not be the same as the definition of a "musculoskeletal disorder", however the two are often mixed indiscriminately in the literature on firefighters.[243] The system used by the investigators has not consistently distinguished between acute traumatic events ("injuries") and adverse health conditions arising over time ("diseases"), which is an important distinction in workers' compensation and for prevention. Even so, the data provide a general profile not dissimilar to other highly physical occupations.

Even this distinction is not perfect. Musculoskeletal disorders arising from repetitive strain (tendonitis, carpal tunnel syndrome) seem to be relatively uncommon in the fire service although very common in other occupations; in workers' compensation, they are classified as a "disease". Other cumulative trauma disorders (including noise-induced hearing loss, which is sometimes classified as such because it is considered to be the cumulative result of numerous traumatic injuries to the hearing mechanism) correspond more closely to the common understanding of an injury occurring over time but for insurance purposes are better treated as "disease" because the rubric more easily allows apportionment among employers.

Low Back Pain

Low back pain is also considered a musculoskeletal disorder and chronic low back pain is classified as a "disease" rather than an "injury", although many cases clearly have some biomechanical component, especially in the fire service. Because the acute onset of low back pain in firefighters appears to have more characteristics of an acute injury, it is counted as such in the acute injuries described in the next section.

Low back pain is the most common musculoskeletal disorder in the general population and there is no evidence that firefighters have a higher prevalence or incidence than occurs in other active occupations. When firefighters developed acute low back pain for the first time in the late 1980's, they were found to have been, in diminishing order of risk, cutting into structures, axe work and cutting into walls during overhaul, breaking windows, nozzleman (holding hose) and backup, rescue, and lifting objects. Tasks that were associated with low risk included connecting hose, pulling hose, and training activity, also in diminishing order. This pattern confirms that attributing low back pain primarily to lifting activities is an insufficient explanation but is consistent with a contribution from other biomechanical factors (i.e. torsion, as when breaking a window with an axe) in this selected and often highly fit FDNY population.[244]

The "biomechanical model" of low back pain dominated acute care and rehabilitation until recently. Strength and stamina training of the back and core have been recognized to reduce the frequency and severity of low back pain acute events.[245]

The "biopsychosocial model" of low back came into widespread use in the 1990's. Of interest is that the investigators in this study had a great deal of difficulty with compliance in scheduling interviews, suggesting that at least in the 1980's firefighters did not see low back pain as a priority health concern.

Osteoarthritis

Osteoarthritis is often attributed to heavy physical workload. Firefighters are highly and significantly overrepresented in registries of osteoarthritis of both the hip (2.52, 1.38 – 4.64) and knee. (2.93, 1.32 – 5.46), suggesting a strong occupational association. As a test of the hypothesis that heavy physical load predisposes to osteoarthritis at both sites, the investigators

found higher frequencies generally among physically demanding jobs, including mail carriers, and noted a particularly strong association with farming.[246] Some forms of osteoarthritis may have a hereditary or susceptibility component, as do many other disorders in this category, and apportionment to occupational stresses and loading is always a controversy for this diagnosis, but for insurance and compensation purposes these cases are generally treated as diseases, rather than injury occurring on a substrate of personal risk.

INJURY (ACUTE RESULTING IN DISABILITY)

Injury leading to compensable disability or death is all too common in the fire service. There is no available or speculative technology that would substantially remove or mitigate the inevitable hazards of the fire scene: structures are consumed and weakened, temperature extremes (mostly heat but also cold in wet winter conditions), uneven surfaces, poor visibility, cumbersome but necessary protective equipment, and work efforts close to the extremes of human endurance and capacity. It has been observed that firefighters accept a thin margin of operational safety protecting them from potentially fatal injury.[247]

The predominant type of injury is minor trauma (over one-third), the most characteristic (almost unique to firefighters) is burns, and heat exposure.[248,249] The least common injury type for firefighters among common injuries shared by public service occupations generally is vehicular accidents, a discrepancy that probably represents the sturdiness of engines and separation in the study from emergency medical technicians, who are at much higher risk.[250] The reasons for these trends are obvious and so will not be dwelt upon in this report.

For in-service injuries, the circumstances are generally documented. There are some overall trends reported in the literature that bear directly upon the fire service and should be noted. Although not separately studied in most studies, chronically disabling injuries are almost certain to show the same relationship as acute injuries with short-term disability.

As many as one-third of injuries in the fire service are the result of exercise, rather than occurring in the line of duty.[249] This reflects the decrease in the number of structural fires, the improvement in safety and equipment effectiveness, and the introduction of mandated and voluntary fitness programs in many fire departments. Since firefighters are often highly competitive and athletic, programs designed to keep them fit are often seen as invitations to

engage in rigorous and competitive regimens, which may increase the risk of injury. (Particularly for weight-lifting, in the author's observation.) Firefighters who exercise have a much higher risk of on-duty injury than those who did not; however they had a much lower risk of non-exercise-related injury. In other words, mandated exercise programs increase the rate of injuries occurring on site from the exercise program but appear to protect against injury in the line of duty. The most significant risk factor for injury while exercising on duty was maximum pull weight as a fraction of body weight (4.03; 1.48 – 10.97), suggesting that weight training may be overdone by members who are already highly trained and may be exceeding their capacity.[248] Thus it may be concluded that mandatory or voluntary exercise may be strongly protective against injuries in the line of duty but incurs a cost in the form of more frequent, largely (but not all) minor exercise-related injuries that may result in temporary impairment.

Various modalities of exercise and training are protective against the frequency and severity of injuries. Core strength training, which seeks to stabilize the trunk, was demonstrated to reduce the frequency (by 44%) and severity (62% reduction in lost time injuries) of injuries in firefighters in what was basically a time series in which each firefighter served as his or her own control. Small but significant effects resulting in increased risk were observed for female gender, prior injury, and especially age.[251] Flexibility training, in particular, has been demonstrated to reduce the severity, although not the frequency, of joint injuries among firefighters.[252] This is not unique to firefighting, of course.

The biomechanical factors that predispose to injury in firefighters are well known. For slips, trips, and falls, factors include personal factors such as body mass, fatigue, experience, and training, and occupational factors such as heavy and bulky personal protective equipment, impaired vision, heat stress, and slippery, uneven, or unstable surfaces.[253]

An important risk factor that cuts across various types of injury and associated with fatalities is time pressure, which is associated with a higher ratio of fatalities per turn-out events except, when there is a human rescue involved. When human rescue is involved, the proportion of firefighter fatalities is low, implying that firefighters are acting carefully when protecting or rescuing people despite time pressure, but are not so cautious, and perhaps are even impatient, when they are working under time pressure to protect property.[254]

Obesity is a major risk factor for injuries resulting in absence among firefighters, with a BMI-related increase in risk on the order of three to four depending on obesity category.[255] There

are many obvious ergonomic reasons why this might be the case, among them lower back and core muscle endurance[256], increased effort requirement, physical bulk, and impaired heat transfer.

Aging is associated with a reduction in the frequency injuries among firefighters, not only with frequency but with re-injury rates and circumstances of injury. Older firefighters (40 to 44) tended to experience more falls from height, slips and falls, and incidence during rapid movement.[257] The authors suggest that the reactive behavior of older firefighters may modify their experience, being more cautious, possibly more aware of their limitations and of unsure footing, and using their accumulated experience to guide them in protecting themselves. This lends empirical support and a new twist of meaning to the old saying that "There are old firefighters, and there are bold firefighters, but there are no old, bold firefighters."

Female firefighters experience a higher rate of injury than male firefighters, historically.[258] However, these studies are relatively old and may not reflect current selection, training, and recruitment practices. The conventional explanation for the finding is that women, on average, are smaller and have less upper-body strength than men, and are more likely to have diminished health capacity affecting performance with age[259], and so are therefore at a disadvantage when full strength is required or when exerting force in awkward situations. However, this explanation is based on averages. Women in the fire service are selected and so it is not clear that such generalizations would apply. These data, while useful and valid for their time, are now ten years old and may or may not be valid given the introduction of performance-nased physical testing and other efforts to create gender-neutral preplacement screening for the fire service. What is needed, if the issue requires further investigation, is a comparative study of injury rates for subjects at comparable levels of performance.

Self-reported depression was a highly-significant risk factor for injury.[248] Personality types are associated with increased frequency and severity (mostly, duration) of injury, as is the case in the general population. Depressed, anxious, and asocial personality types are at greater risk, but since there are also behavioural correlates to these personality profiles (such as alcohol and substance abuse), and therefore a strong potential for confounding, personality type cannot be easily used for prediction and to do so in individual cases would raise serious issues of employment law and fairness.

A past history of smoking was a powerful risk factor for injury (1.8; 1.31 – 2.99; smokeless tobacco was slightly elevated but did not achieve statistical significance (1.19; 0.70 – 2.04).[248]

Turnout gear and other equipment impede physical movement and may throw the firefighter off balance and reduce postural stability, especially when fatigue sets in after a long work shift.[260] This is not surprising, and until there is a breakthrough in materials for protective gear, not particularly useful but confirms conventional wisdom.

Against this background of risk factors and hazards, it may be surprising that there are as few injuries leading to incapacity as there are. Even so, injuries are common and, as in all occupations, distributed unequally with minor injuries being most frequent and severe or permanently disabling injuries fortunately relatively uncommon. In 2009, the injury rate for all US firefighters was 6.8 injuries per 100 firefighters per year, with suspected underreporting. Table 5 summarizes the distribution of injuries and comments on their tendency toward severity from a recent study[249], which is consistent with other sources.[243]

Table 5. Distribution of types of injury among firefighters.[249]

Injury Type	*Fireground (%)*	*Exercise (%)*	*Comments*
Soft-tissue ("muscle") injuries (sprains and strains)	40.2	85.2	
Contusion, laceration	26.1	7.7	
Burn	15.2	0.0	Also occurs during training.
Penetration, piercing	5.4	0.3	Includes needlestick injury.
Eye	4.4	0.3	
Inhalation	4.4	0.0	
Electrical	2.2	0.0	
Fracture	2.2	4.7	
Medical emergency	0.0	1.7	

As noted, burn injuries are the occupational injury category unique to firefighters among public safety professions. In a series of 982 cases admitted to New York Presbyterian Hospital between 1992 and 2002, frequency of serious burns fell abruptly early in the decade, reflecting regional trends, and then plateaued for the last seven years, with some variation. Relative to serving as an officer (10%), burn injuries were more often associated with nozzle and back-up positions (50%), where holding the hose and being exposed to return spray may expose the firefighter to scalding hot water, and with search and rescue (16%). It is perhaps reassuring with respect to professional competence that very few firefighters received burns from cooking at the fire hall (3%). However, this database did not report injury rates, only proportions and only covers burns that were severe enough to require admission; it also did not evaluate fatalities separately (there were three in hospital). The most common anatomic parts burned were the lower extremities (37%), especially among nozzlemen, but not the feet (1%), and the head and neck (25%).[261]

Reflecting a lower level of severity, burns treated in an outpatient clinic at the same institution from 2000 through 2002 showed a similar pattern, except for fewer burns to the lower extremities (because "nozzleman burns", being scalds, tend to be severe and require admission).

RECOMMENDATIONS

What These Recommendations Mean

Recommendations on the recognition of disorders for purposes of compensation must be made primarily on the basis of evidence available at the time and on the terms of reference that apply to their formulation. Human studies (mostly in the form of epidemiology) are preferred as evidence but narrowly relevant studies are often unavailable, in which case collateral evidence must be sought from toxicology and clinical medicine. As the evidentiary base grows, recommendations will change. Because the evidence is almost always added to and only rarely subtracted from (for example, when a finding is later disproven or there is a reevaluation, such as occurred with birth defects) the list of candidate conditions tends to increase over time. Dropouts are unusual because new studies tend to add nuance rather than contradict earlier findings (particularly with respect to the cancers).

In this report, the guiding principle for evaluation is the weight of evidence, giving priority to human studies but taking collateral evidence into account as needed. The standard employed is not scientific certainty, which is inappropriately stringent in this application, and is also less stringent than would be required for a legislated presumption (evidence for at least a doubling of risk).

Finally, it should be noted for readers unfamiliar with compensation policy that the alternative to accepting a particular diagnosis as qualification for compensation is not to reject all claims for the diagnosis. There are innumerable special and unique situations that arise in compensation review. If a condition is not recognized as compensable, the alternative is to examine the particulars of the individual case to see if there are grounds to conclude that the condition arose out of work.

Recommendations

The following recommendations for recognition of chronic conditions associated with firefighting are offered on the basis of the *weight of evidence*. The alternative to recognizing a particular diagnosis as compensable is to examine the particulars of the individual case.

1. Conditions demonstrating elevated risk among firefighters, weight of evidence sufficient to make a recommendation on general causation:

- Heart attacks following an alarm or knockdown by up to 24 to 72 hours, resulting in disability
- Acute respiratory failure and decompensation within 24 hours of an event (toxic inhalation, pulmonary edema), resulting in disability
- Asthma, irritant induced (associated with a particularly intense event or exposure history)
- Bladder cancer
- Kidney cancer
- Testicular cancer
- Lymphoma (Diffuse large B-cell lymphoma and follicular cell lymphoma; others unclear and require individual analysis)
- Leukemia (Acute myeloid leukemia)
- Brain cancers (Glioma is most likely to be related to firefighting)
- Lung cancer in a firefighter with little or no smoking history
- Mesothelioma
- Cancer of the lip
- Breast cancer among males
- Amyotrophic lateral sclerosis
- Noise-induced hearing loss
- Post-traumatic stress disorder and reactive depression (requires compatible history and diagnosis)

2. Conditions for which elevated risk of firefighters is suggested by the current weight of evidence: but which require qualification in a recommendation on general causation

- Accelerated decline in lung function in a non-smoker usually not associated with impairment; history of inadequate respiratory protection)
- Asthma, irritant –induced (sufficient to cause respiratory impairment)
- Chronic obstructive airways disease with minimal or no smoking history (fixed airways obstruction, *not* "chronic obstructive pulmonary disease" as term is generally understood)
- Colon cancer (for individuals with a low *a priori* risk)
- Melanoma (taking into account sun protection, lifestyle, and location)
- Myeloma (overall; cannot differentiate by type at the present time)
- Parotid gland tumours (suggest case-by-case evaluation)
- Nasal sinus cancer (in the absence of other exposures)
- Traumatic injury resulting in impairment leading to disability (must be individualy considered)
- Musculoskeletal disorders (chronic) resulting in impairment leading to disability (must be individually considered)

4. Conditions for which evidence of elevated risk of firefighters is not sufficient to make a provisional recommendation on general causation – individual evaluation is recommended

- Sarcoidosis
- Thyroid cancer
- Esophageal cancer
- Basal and squamous cell carcinomas (taking into account sun protection, lifestyle, and location)
- Laryngeal cancer
- Prostate cancer (below age 60)
- Infectious disease

3. Conditions for which evidence of elevated risk of firefighters is not sufficient to make a provisional recommendation on general causation but association is unlikely – individual evaluation is recommended

- Prostate cancer (above age 60)
- Glomerulonephritis
- Infertility and birth defects in offspring (particular reference to heat exposure during pregnancy)

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QUALIFICATIONS OF THE AUTHOR

Tee L. Guidotti, MD, MPH, FRCPC, FCBOM, FFOM, DABT

Tee L. Guidotti has been involved in studies on the toxicology of combustion products since 1973 and on firefighters since 1985, when he began a research project on municipal firefighters in Alberta as a means of building a research team for the new Occupational Health Program he established at the University of Alberta. Over the years, his work also branched into issues of the adjudication of compensation claims for firefighters and the scientific basis for scheduled presumption. His work on cancer presumption, based on a "balance of probabilities" approach grounded in public policy, was adopted by legislatures and workers' compensation agencies across Canada and in several American states. His work has also involved emergency medical services, hazmat, and emergency management. He is also well known for his work on hydrogen sulfide and other hazards in the oil and gas industry. Since 2002, he has been involved in studies of emergency responders to the World Trade Center tragedy of 11 September 2001. He has been consulted on the design of major study of firefighters, such as the Australian national study currently underway and the recent study by the National Institute of Occupational Safety and Health (US). He is currently collaborating on a study of industrial firefighters in the oil and gas industry.

A retired academic, Dr. Guidotti is now an international consultant in occupational and environmental health and medicine working primarily in the US, Canada, and the Middle East through Medical Advisory Services (a division of the NMAS Group), with offices in Rockville, Maryland (USA). Dr. Guidotti currently holds the title of Vice-President for HSE and Sustainability (HSE is "health, safety, and environment") at MAS, which describes his area of consulting practice. He lives in Washington DC. He is a dual citizen of Canada and the United States.

Dr. Guidotti retired in 2008 as Professor and Chair of the Department of Environmental and Occupational Health in the School of Public Health and Health Services, The George Washington University Medical Center, Washington DC, and Director of the Division of Occupational Medicine and Toxicology in the School of Medicine and Health Sciences. Prior to taking this position in 1999, he was for 15 years Professor of Occupational and Environmental Medicine and Director of the Occupational Health Program in the Department of Public Health Sciences at the University of Alberta in Edmonton, Canada, where in 1996 he was named a Killam Annual Professor.

Dr. Guidotti earned his MD degree in 1975 from the University of California at San Diego, his MPH from The Johns Hopkins School of Hygiene and Public Health in 1971, and spent two years in research training at the National Institutes of Health. He trained in clinical medicine at the Johns Hopkins Hospital and is board certified in the U.S. in both internal medicine (board-certified) and pulmonary medicine. He also trained in occupational medicine at Johns Hopkins and holds fellowship specialty credentials in that specialty Canada (FRCPC, FCBOM), board-certification in the U.S. (ABPM) and the UK (FFOM). He is also a diplomate of the American Board of Toxicology (DABT), the principal credential for research and regulatory toxicologists (i.e. not clinical medical toxicology), and holds the QEP (Qualified Environmental Practitioner (an environmental management qualification) specializing in air quality.

Dr. Guidotti's research interests include occupational and environmental lung diseases, air quality studies, and inhalation toxicology. He is best known in occupational medicine for his expertise on the occupational health problems of firefighters and oil and gas workers. His other interests include inhalation toxicology, air quality studies, ecosystem health, risk science, and the evaluation of scientific evidence in law, workers' compensation and public policy.

Dr. Guidotti is the author or coauthor of over 300 publications, and has written or edited six books, including a textbook, a monograph on the evaluation of scientific evidence in law and public policy, and a handbook for occupational health services. Dr. Guidotti is the Editor in Chief of *Archives of Environmental and Occupational Health*, a historically important journal founded in 1919.

Dr. Guidotti has chaired and served on committees of the Institute of Medicine (National Academies of Science), the Council of Canadian Academies, the Royal Society of Canada, Health Canada, and the US Department of Homeland Security, and he chaired the committee of the American Thoracic Society that revised the diagnostic criteria for asbestos-related disease (specifically, asbestosis) in 2007. He is a Past President of both the American College of Occupational and Environmental Medicine and the Association of Occupational and Environmental Clinics. In 2013, he was recognized with the William S. Knudsen Award for Lifetime Achievement in Occupational and Environmental Medicine.

Dr. Guidotti is registered as a physician practicing occupational and environmental medicine by the College of Physicians and Surgeons of Ontario and is licensed to practice in the states of California and Maryland and the District of Columbia.

APPENDIX

Table of Studies

(See accompanying document in landscape format.)