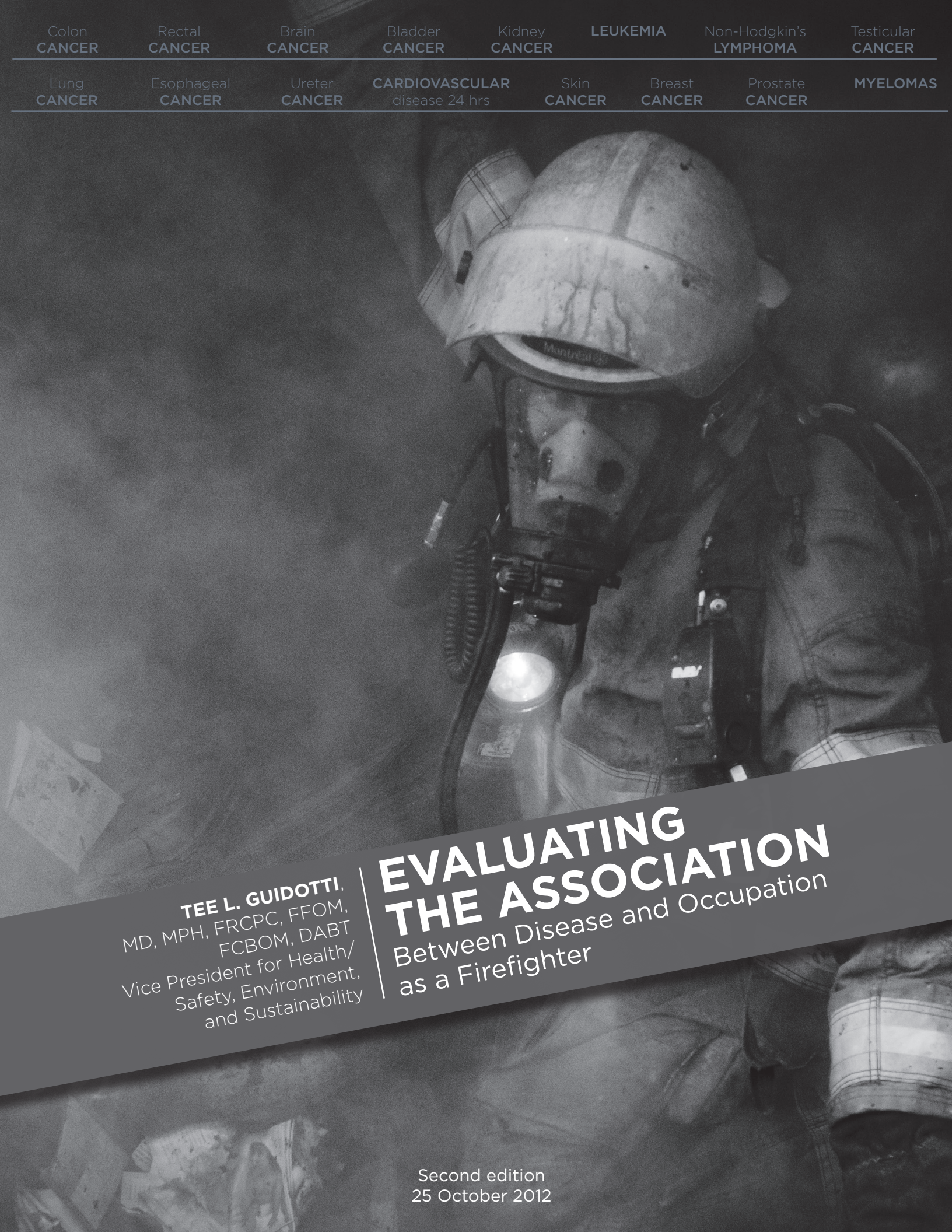

EVALUATING THE ASSOCIATION

Between Disease and Occupation as a Firefighter

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EXECUTIVE SUMMARY

This report is prepared for the RAPQ for the purpose of examining the current evidence for risk of certain diseases associated with the occupation. The diseases of concern are cardiovascular disease (primarily heart disease), cancer (particularly selected cancers). The task if this evaluation involves three steps: 1) an evaluation of the evidence for general causation (the demonstration that the disease outcome is a risk associated with work as a firefighter, either by direct or indirect cause), 2) an evaluation of the strength of the evidence, taken as a totality, in support of a rebuttable presumption (the policy that unless there is compelling evidence to the contrary, a claim from a firefighter for compensation for a particular outcome will normally be accepted), and 3) identification, when possible, of factors that apply to specific causation, the individual characteristics that make apportionment of cause to firefighting more or less likely.

BACKGROUND

Workers' compensation acts as they are applied to firefighters, legislated presumptions, and current workers' compensation policies are based on the known hazards of firefighting, the known and assumed risk of certain disease outcomes among firefighters, and the recognition that such presumptions are necessarily based on a level of certainty that is not the same as scientific certainty.

The movement for presumption with respect to cancer began with the Legislative Assembly of Manitoba in 2001. The Workers' Compensation Board of Manitoba requested our assistance in evaluating the association of specific types of cancer with firefighting at the time that this was proposed by MLAs in that province, as a result of work on the issue originally performed in Alberta. An Act was adopted, followed a short time later by other provinces, so that now seven of the ten provinces (excepting Newfoundland and Labrador, Prince Edward Island, and Quebec) and the three territories have adopted presumptions. The state legislatures in most American states have presumptions for heart disease and most now have specific presumptions for selected cancers. The rational for accepting claims for selected cancers has also found increasing acceptance in workers' compensation adjudication in Canada and the US, but less often for cardiovascular disease, in part because many states had already adopted presumptions for heart attacks.

EXPOSURE

To be sure that a disease is associated with an occupation, it is not always necessary to know the exact cause scientifically. However, identifying a responsible toxic exposure lends support to the conclusion, is an important factor in assessing an association in epidemiology as putatively causal, and is required in some jurisdictions for compensation.

Firefighters are exposed to a number of hazardous chemicals associated with combustion that are known to be toxic to the heart. Chief among these are carbon monoxide and cyanide, but others have been identified recently, particularly ultrafine particulate matter, and some are only now becoming appreciated with respect to their potential contribution, such as perfluorooctanoic acid (PFOA). Complicating the issue among firefighters is that heart disease is the leading cause of death in North America and the average levels of cardiovascular risk factors that characterize firefighters have not been shown to be much different than for the general population. The analysis must therefore go beyond superficial averages and probe more deeply into the evidence. Firefighters may be at risk for a number of exposure-related cancers because of their demonstrable occupational exposure to a variety of toxic agents, of which the most significant for cancer risk are polycyclic aromatic hydrocarbons (PAHs), asbestos, benzene, 1,3-butadiene, dioxins and furans, and vinyl chloride; formaldehyde may also be significant. Individual fires may contribute substantial additional exposure, however, such as polychlorinated biphenyl compounds (PCBs). 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.

First responders, particularly firefighters of the Fire Department of New York, to the World Trade Center disaster on 11 September 2001 sustained exposures that were very different from those typical of professional firefighters and there is evidence that their health experience is different from that of other firefighters as a result. As a result, this report does not cover or reflect the experience of FDNY firefighters who responded in the event.

APPROACH

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 unresolved issues remain, especially whether firefighters are at increased risk for certain cancers and for cardiovascular disease. This is not a deficiency of the literature. It reflects the inherent limits of applying the science of epidemiology to adjudication rules.

The evidence for excess of cardiovascular disease and for certain cancers has been unclear until recently. This has led to considerable controversy and inconsistency in the adjudication of claims for occupational disease. For cardiovascular disease, the problem has been complicated by the high background rate of cardiovascular disease, especially heart disease, and problems with benchmarking the risk. For cancer, there are different and clearer scientific reasons why the elevated risk for selected cancers has been difficult to demonstrate. 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. When they are not, the validity of study design and power of the more substantial positive and negative studies are more persuasive than meta-analysis.

Such presumptions must meet legal standards of the weight of evidence, in two ways. First, the association with work must be supported by the literature on the balance of probabilities ("more likely than not", or >50% certainty), but not necessarily to a level of scientific certainty (conventionally assumed to be >95% certainty). Second, it must be more likely than not in the unselected individual case coming to adjudication, that the condition arose out of work, which corresponds to an approximate doubling of the relative risk. Factors specific to the individual case are grounds for rebuttal, or challenge to the presumption. The presumptions for bladder cancer and kidney cancer are grounded on substantial evidence that already approach scientific standards of certainty. The presumption for testicular cancer is based on an emerging literature that strongly suggests a high risk but illustrates the "first case" problem: the first case of a previously unrecognized work-related condition to come to adjudication is likely to be denied because the literature does yet not exist to support it. The presumptions for brain cancer, non-Hodgkin's lymphomas and leukemias are based on the inference that within the overall category there are specific disorders for which the evidence suggests an elevated risk but it is not possible to discern which specific diseases are in excess. There is indirect but strong evidence for an elevation in risk of lung cancer for nonsmoking firefighters but in smoking firefighters the risk from firefighting would be overwhelmed by the risk from smoking. The argument for a presumption for nonsmoking firefighters with lung cancer may also apply in some cases to colon cancer.

These issues illustrate more appropriate approaches than conventional analysis to applying epidemiological data to these problems in the individual case or claim. The use of these approaches acknowledges both that scientific standards of certainty do not apply to the individual case because the legal requirement is for determination on the basis of the weight

of evidence and that conventional practices in epidemiology are inadequate to assess the risk of rare diseases accurately, particularly when they are aggregated into medically meaningless rubrics.

Even with application of this new approach, there are some disease outcomes for which the evidentiary base is simply inadequate to form a judgement to support recommendations for general causation and presumption. In such situations, the "default" is always evaluation of the individual case in light of the evidence available at the time.

CARDIOVASCULAR DISEASE

For many years there has been concern that firefighters are at greater risk of heart disease than men (throughout the history of firefighting, firefighters have been overwhelmingly male) in other occupations. Some jurisdictions (including 43 American states) have incorporated that assumption into legislation to compensate firefighters for heart attacks and now recognize heart attacks within 24 hours of an alarm as being work-related (the criterion of the National Fire Prevention Association). This criterion is overly stringent and should be revised.

Activities related to firefighting can clearly precipitate a heart attack. However, it has been difficult to demonstrate general causation for mortality from heart disease among firefighters against the high background of mortality from cardiovascular disease, which is the leading cause of death in North America. There is now strong evidence that work-related activities may precipitate myocardial infarction in firefighters with pre-existing coronary artery disease. There is also strong evidence that mortality may take special forms and may have unique associations arising from work as a firefighter as a result of work-related exposures, particularly carbon monoxide but also cyanide and other products of combustion.

Whether the underlying risk of cardiovascular disease is elevated among firefighters generally remains controversial. Firefighting is an occupation that requires high levels of fitness for safety and performance. However, fire departments only recently adopted stringent requirements for fitness to work and often do not apply them rigorously to veteran firefighters, who are in any case likely to be older, than new hires. As a consequence, current data on cardiovascular fitness among firefighters reflect a mixed population and may underestimate risk for older firefighters while overestimating risk for younger firefighters.

CANCER

Certain types of cancer present unique issues and methodological problems in interpreting epidemiological data: brain, bladder, kidney, non-Hodgkin's lymphoma (often referred to as "lymphatic cancer") together with myeloma and leukemia (sometimes referred to as "haematopoietic cancer"), lung, prostate, melanoma and thyroid. General guidelines for latency and elapsed time are discussed in the text.

Evidence available since 1994 suggests that it is reasonable given the available scientific evidence to adopt a policy of presumption for brain cancer, bladder cancer, kidney cancer, non-Hodgkin's lymphoma (lymphatic cancer), myeloma and leukemia (haematopoietic cancer) for claims associated with occupation as a firefighter. Factors specific to the individual case are grounds for rebuttal, or challenge to the presumption. The presumptions for bladder cancer and kidney cancer are grounded on substantial evidence that already meet scientific standards of certainty. The presumption for testicular cancer is based on an emerging literature suggesting a

high risk but illustrate the "first case" problem: the first case of a previously unrecognized work-related condition to come to adjudication is likely to be denied because the literature does not exist to support it. The presumptions for brain cancer, non-Hodgkin's lymphomas and leukemias are based on the inference that within the overall category there are specific disorders for which the evidence suggests an elevated risk but it is not possible to discern which are in excess. The argument for a presumption for nonsmoking firefighters with lung cancer may also apply in some cases to colon cancer.

Prostate cancer presents a different problem. Firefighters have been shown to have an elevated frequency of incidence of cancer of the prostate in the US but it is likely that this is the result of a screening bias. The disease is known to be under-diagnosed in the general population because most cases are indolent and discovered only incidentally. Firefighters, however, are typically screened for the disease as part of more regimented and comprehensive health services. As a result, one would expect increased detection of prostate cancer compared to the general population without necessarily a true increase in incidence. The evidence supports this explanation for studies that show an increased incidence, rather than a causal association between prostate cancer and firefighting.

Firefighters have been shown to have an elevated frequency of melanoma, an uncommon but highly malignant skin cancer, but it is unclear whether this is the result of sun exposure, which is the usual risk factor, or some other hazard. The association is likely to be clearest for wildfire fighters since they are most likely to be exposed to sun during the course of their workday. This disease is very aggressive and is not likely to be overlooked or misdiagnosed in studies, so the issue is not one of validating the association but in assessing causation as arising out of firefighting. No conclusion can be reached at this time.

Thyroid cancer has been reported to be elevated among firefighters. The evidence is not sufficient to make a recommendation at this time.

RECOMMENDATIONS

The following recommendations are offered:

1. **Conditions for which a Presumption is Justified by Current Evidence**

    - Heart attacks following soon after an alarm or event (up to 24 to 72 hours)
    - Bladder cancer
    - Kidney cancer
    - Testicular cancer
    - Lung cancer in a non-smoking firefighter
    - Non-Hodgkin's lymphomas (Current knowledge precludes differentiating by type)
    - Myelomas (Current knowledge precludes differentiating by type)

2. Conditions for which a Presumption is Justified with Qualification

- Brain cancers (Glioma is more likely than other types to be related to work)
- Leukemias (Acute myeloid leukemia most likely)

3. Conditions for which an Association but Not Presumption is Suggested by Current Evidence

- Lung cancer (rebuttable based on smoking history)
- Colon cancer (for individuals with a low *a priori* risk)
- Melanoma (for firefighters who mostly work outdoors, such as wildfire fighters)

4. Conditions Requiring Further Evaluation (Insufficient Evidence to Make a Recommendation)

- Thyroid cancer

INTRODUCTION

Whether firefighters are at increased risk for cardiovascular disease, lung diseases, and for particular cancers has been an active topic of investigation for many years. These issues are part of a broader discussion on health in firefighting involving health risk, protection of public safety professionals, and equitable compensation.[1]

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, sustained interest and relative completeness of data, there are many unresolved issues which will remain for years to come because statistical certainty is unachievable. Since adjudication decisions cannot be postponed, many issues will continue to require resolution by inference and judgment.

Some contentious issues will find resolution one way or another from the multicentre study of firefighters currently being organized by the (US) National Institute for Occupational Safety and Health, but implementation and analysis of data from this massive effort will take years and will face some of the same limitations of current studies. Decisions on providing protection for firefighters' health and for eligibility for compensation cannot wait, however.

Many and perhaps most of the open issues with respect to cancer and other "rare" diseases (in the biostatistical sense of rare) are also unlikely to be entirely resolved even by much more extensive data.[2] This is in part because some cancers of interest, such as the individual members of the non-Hodgkin's lymphoma rubric, are individually so uncommon that even very large studies of the future will have statistical uncertainty and because classifications of cancers into groups relevant to etiology change, sometimes, again in the case of lymphomas, frequently. Furthermore, interpretive issues grounded on attribution (in the formal, epidemiological sense) and apportionment (in the individual case, or disability or compensation sense) will remain.

Firefighters may be at risk for heart disease because of their exposure to several cardiotoxic exposures at a time when they are experiencing high levels of cardiac demand and at risk for a number of exposure-related cancers because of their occupational exposure to a variety of toxic agents.[2-7] A major hypothesis is that risk increased following the introduction in the 1950's of combustible plastic furnishing and building materials known to generate toxic combustion products which may be, variously, cardiotoxic or carcinogenic. However, the evidence for excess of heart disease or certain cancers has been equivocal, with different results in different studies. This has led to great controversy and inconsistency in the adjudication of claims for occupational disease. The practical importance of this question, together with its scientific interest, has led to increasing attention being given to firefighters' cardiovascular health over the last decade and to cancer risk over the last three decades.

The incremental addition of increasingly well-designed and well-conducted studies on firefighter health has been welcome and very useful in guiding decision-making. Every new study brings some degree of replication, some differences reflecting the specific population of firefighters and the communities from which they are drawn, local patterns of occupational hazard such as housing stock, and some methodological differences that allow comparison among studies.

Most large studies on firefighters are similar in design and face similar limitations on power for rare outcomes. However, they often have differences, sometimes subtle, that can be used to drill down to investigate particular problems by examining subgroups, exposure-response relationships, revealing anomalies, and confounding by smoking.

Meta-analysis has been performed in an effort to overcome some of these limitations. However, the experience applying meta-analysis to studies of firefighters has not been satisfactory overall and this approach does not provide sufficient guidance. 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

In 1994, the Industrial Disease Standards Panel of Ontario[8] produced a widely-quoted report designed to identify candidate conditions for occupational disease presumptions in workers' compensation. We published a similar analysis in 1995[5], with conclusions reached independently. We thought at the time that certain cancers were likely to be associated with firefighting: lung cancer, genitourinary cancers (kidney, bladder), brain, lymphatic and hematopoietic, colon and rectum. In that paper, the strengths and weaknesses of the evidentiary base were thoroughly explored. The older studies will not be critiqued in detail here except insofar as they are specifically relevant to the present discussion. More evidence became available in the years following, which tended to strengthen these conclusions and to recognize other possible associations.

In 2002 we prepared a report[9] on the health risks to firefighters for the Government of Manitoba at the request of the Minister for Labour and Immigration, who is also responsible for the Workers' Compensation Act, The Hon. Becky Barrett. Based on that report, Bill 5 was introduced into the Manitoba Legislature to facilitate claims for certain chronic diseases (stated as cancers of bladder and kidney, cancer of the brain, haematopoietic cancers and lymphatic cancers) and was passed into law. The report was also mentioned by the Lieutenant Governor of Manitoba, The Honourable Peter Liba, in his Speech from the Throne in November. This report garnered

much attention in the press and from other governments. The Workers' Compensation Board of Manitoba later requested further guidance on the adjudication of claims involving certain types of cancer. This guidance was intended to support proposals for the amendment of the Workers' Compensation Act with respect to establishing presumption for occupational disease among firefighters.

There were three parts to the review. The first was to identify evidence for an association that was sufficient in magnitude and circumstances to be causal and not appreciably confounded. The second was to evaluate whether the magnitude of the association, in context, was consistent with equal odds, or a doubled risk compared to an unexposed reference population. The third was to advise on latency periods that would be deemed plausible for work-related cancers. For firefighters, as for most occupations, the only practical basis for such a criterion is duration of employment. We did not advise on criteria for specific job assignments or cumulative number of alarms for fire stations to which firefighters were assigned, as these are generally not well documented.

Manitoba did adopt presumptions for selected cancers among firefighters in 2003. The province started this wave of interest because of a strongly-held belief that public safety workers, like those who defend the country militarily, should be compensated and their families protected from the consequences of the extraordinary risks they take. The feeling was that this should be done expeditiously and without an adversarial process.

We subsequently updated the review and elaborated on several points in a report prepared for the British Columbia Professional Firefighters Association (BCPFFA), which subsequently led to the provincial legislature of that province adopting a presumption. We have also submitted briefs to the workers' compensation boards and tribunals of Alberta and British Columbia (before the BCPFFA report) and given testimony in American state legislative hearings (notably Vermont and Oregon) for the same issues.

In 2007 we published a detailed paper on selected cancers that defined a different approach to looking at the problem.[10] The present report is in some ways an expansion of that paper and an extension of its logic into cardiovascular disease. In 2011, we were asked by the Regroupement des associations de pompiers du Québec (the Coalition of Associations of Quebec Firefighters) to prepare a report on selected disease outcomes in firefighters (cardiovascular disease, cancers). The present report is an update of that report and further revision and expansion, sponsored by the RAPQ, recognizing several important advances since the first edition.

Throughout this process we have also had the opportunity to evaluate many individual cases and to review many claims of cancer among firefighters, less often cardiovascular disease. Some of our reviews have not supported claims for compensation. This experience reviewing individual cases has provided a rich experience that puts the statistical data in context. It became very clear in reviewing these cases, for example, that it is generally beyond the means and capacity of any one applicant for compensation to make a complete scientific case for a newly recognized or incompletely investigated disease, even if evidence for causation is present. One of the most compelling reasons for adopting presumptions when they are warranted by the evidence is to relieve injured firefighters and their families of this burden and obstacle.

Existing presumptions

In Canada, legislated presumptions for selected cancers have been adopted by seven of the

ten provinces, the exceptions being Newfoundland and Labrador, Prince Edward Island, and Québec, and all three territories. Presumptions for cardiovascular disease are limited to "heart attacks" occurring within 24 hours of duty, and have been adopted by five provinces (but not by Nova Scotia, Newfoundland and Labrador, Prince Edward Island, British Columbia, or Québec) and all three territories.

According to the National League of Cities (NLC)[11], which generally opposes presumption for firefighters and other public employees, many jurisdictions (including 43 American states) have incorporated that assumption into legislation to compensate firefighters for heart attacks and now recognize heart attacks within 24 hours of an alarm as being work-related (the criterion of the National Fire Prevention Association). As noted above, the movement for a presumption for selected cancers has spread to at least 35 American states, and resulted in legislation being passed in 26 of them to establish rebuttable presumptions for compensation of firefighters who develop certain types of cancer. These acts and current workers' compensation policies are based on the known hazards of firefighting, the known and assumed risk of certain disease outcomes among firefighters, and the recognition that such presumptions are necessarily based on a level of certainty that is not the same as scientific certainty.

In 2009, the NLC published a report[11] questioning the association between firefighting and cancers, based on the findings of a contract research company that reviewed the literature. This report did not address the most important aspects of our previous work: the fundamental issues of methodology, the standard of certainty, the intrinsic sources of bias, power and the consistency of studies of rare outcomes, and the internal evidence for exposure-response that had been demonstrated in the stronger studies. The NLC represents the employers of municipal firefighters and so this report can be seen as an attempt to rebut evidence in support of a presumption. Despite heavy publicity, it did not effectively do so.

The "first case" problem

The burden on the applicant is particularly severe when a case is the first of its kind or is based on new and incomplete evidence. This "first case" problem has the effect of shifting the burden of proof back to the claimant, despite the provision in most workers' compensation acts that the benefit of the doubt will be given to the worker. It is also generally beyond the means and capacity of any one applicant for compensation to make a case to a standard of scientific certainty, even for common and generally accepted outcomes, such as myocardial infarction while on duty during an event, because of compounded uncertainties in the individual case. Likewise, it is almost impossible for any one applicant for compensation to make a case to a standard of scientific certainty for a "rare disease", one that has an infrequent outcome, because studies will always, by their nature, be inconsistent. It is almost impossible for any one applicant for compensation to make a case to a standard of scientific certainty for a common disease, one that represents a significant elevation in risk against a background of high frequency in the population. By the time one rules out these options, it is clear that the burden of proof weighs very heavily indeed on the claimant community.

The problem is not with these cases. Some cases naturally have merit and others do not. It is with the application of inappropriate scientific standards, in which only near-certainty is admissible, to a best judgment on the basis of the weight of evidence in the presence of uncertainty, which is how disputes outside of science are normally resolved and which was the standard originally intended for adjudication as written into workers' compensation acts in North America.

THE RATIONALE OF ADJUDICATION

The logic of assessing causality in adjudication is not the same as for concluding causation in a scientific investigation, where the minimum standard of certainty is nominally 95%, or in a criminal prosecution (where the standard is "beyond reasonable doubt", sometimes characterized as 99% sure). In civil litigation and in almost all adjudication systems, experts are neither required nor expected to prove causation to a near certainty.[10, 12, 13]

In adjudication and civil litigation, the burden on the claimant or plaintiff is to determine whether it is more likely than not that the evidence favours one side or the other. In worker's compensation, experts are required to provide evidence for or against the proposition that the claimant's injury arose out of work and to determine the weight of evidence. All hinges on the weight of evidence in the individual case. In most jurisdictions in North America, including Québec, the acts are written so that the benefit of the doubt is given to the claimant if the odds are even.) In workers' compensation, the weight of the available evidence, which is usually incomplete, must support a decision that it is more likely than not that the claimant's condition arose out of work.

The near-universal standard of the "weight of evidence" for certainty is "more likely than not", rather than the conventional 95% level of certainty, the meaning of the standard alpha probability for Type I error (concluding that something is true when it is not), or one in twenty, commonly expressed as $p < 0.05$, for a scientific finding or study. Thus, one obstacle to applying the results of epidemiology to adjudication practice is learning to abandon the conventional notion of certainty one has learned as a scientist, which creates a highly conservative, and therefore reassuring, standard of certainty but one wholly inappropriate to the resolution of claims and disputes in the real world where things are not so clear. In evaluating a claim or as experts in litigation, one is working within a framework in which individual studies may be so judged against a statement of absolute probability but the weight of evidence is evaluated as odds, with greater than equal odds favouring one conclusion over another.

The relationship between risk and the decision to accept a claim or to adjudicate in favour of a particular claimant or plaintiff is another step, and not a simple one. Merely demonstrating that there is an elevated risk of a particular outcome among members of an occupational group is not enough to decide the claim. It is also necessary to demonstrate that the individual circumstances of the claimant are consistent with the premise that the condition arose out of work. The weight of the available evidence, which is usually incomplete, must then support a decision that it is more likely than not (with the benefit of the doubt going to the claimant if the odds are even) that the claimant's condition did indeed arise out of work. The factor causing the outcome could be a job-related hazard or circumstances intimately associated with work (such as passive cigarette smoking) but would not normally be a voluntary activity that is not required by the job (such as active cigarette smoking).[12]

It is important to realize that an assessment based on the preponderance of evidence does not represent a distortion of scientific standards. It may be said that evaluating the epidemiological (and other scientific) evidence against a standard of preponderance of evidence is like the practice epidemiology "as if" the standard of certainty were 50+%, and not 95%. However, that is an exaggeration. The preponderance of evidence is required and serves as the ultimate criterion once the evidence is available but the interpretation of the studies is informed by the inferential statistics that have already been applied in the interpretation of each study.

Holding out for evidence of scientific certainty places an unreasonable burden of proof on the claimant, especially in a situation in which scientific certainty probably can never be achieved as a practical matter. Scientific certainty was not designed (as it is a social construct) to resolve disputes over causation in the real world. Rather, it represents a legal requirement and a social convention. Expert witnesses must follow the rules of the court and of procedure, not the rules of scientific inquiry. Experts are not asked, in effect, to practice epidemiology "as if" the standard of certainty were 50+%, rather than 95+%, but to integrate the pieces based on the best available evidence, taking into account uncertainty, and to determine the relative weight in order to come to a conclusion. This is a legal requirement within a system that vests decision-making authority in the court, the adjudicator or a jury, but not the expert.[12]

It is for this reason that the otherwise thoughtful and useful reports prepared by McGregor for IRSST have limited application in adjudication. They are well done and comprehensive as scientific documents but do not address the issue by the standard of preponderance of evidence.[14-17]

The epidemiological literature

Table 1 presents the published overall risk estimates for major categories of disease from the major studies used in the evaluation of risk of firefighters for the diseases listed. It is an expansion of our table first published in 1995.[5]) It is critical from the outset to realize that this table does not tell the whole story, or even half of it. The remainder of this report is devoted to determining what these overall figures conceal, more so than elaborating on what they reveal.

Investigators, adjudicators, and litigators have a major advantage in dealing with issues related to firefighting because the literature is so large. It may therefore seem anomalous that much of this report deals with limits on certainty, insufficient evidence, knowledge gaps, and uncertainty in interpretation. This is because no literature in occupational epidemiology, even one as extensive as this is, truly reflects the complexity of reality on the job.

The 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.
- Exposure-response relationships. In very few studies (e.g. Baris et al.[18] and Guidotti[19]) are exposure indicators reported beyond length of service.
- Disease rubrics. Clinical subtlety in diagnosis is 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 L'Abbe and Tomlinson and reports based on that work[20, 21]). The reason for this is that statistical methods used in epidemiology work better with larger numbers, but statistical methods applied to larger numbers based on illogical combinations do not work particularly well either.
- Disease identity. Developing scientific knowledge, particularly about causation, makes many and possibly most 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.[22] It is highly likely that certain individual lymphomas are caused by different exposures.[22, 23] However, since there are no studies on individual lymphoma types and risk from firefighting, individual lymphomas are relatively rare compared to other cancers which makes such studies inordinately expensive and difficult, and the classification is likely to change again with advances in scientific knowledge, and the ability of epidemiology to identify occupational associations with any certainty is weak, to say the least.

- 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 in the situation of rare diseases and causation. 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.[24])

- 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.

Table 1. Selected Cancer Risk Estimates from Major Studies of Firefighters.

AUTHORS, YEAR	POPULATION	DESIGN	RISK ESTIMATE	LUNG	COLON	RECTUM	BLADDER	KIDNEY	BRAIN	CVD	COPD
Baris et al., 2001[18]	Philadelphia FD	Cohort	SMR	1.13 (0.97-1.32)	1.51 (1.18-1.93)	0.99 (0.59-1.68)	1.25 (0.77-2.00)	1.07 (0.81-1.88)	0.61 (0.31-1.22)	1.01 (0.96-1.07)	0.64 (0.40-1.02)
Bates, 2007[25]	California	Cancer registry	OR	0.92 (0.84-1.01)	0.84 (0.74-0.94)	0.84 (0.74-0.94)	0.79 (0.68-0.92)	0.98 (0.81-1.20)	1.23 (0.97-1.56)	n/a	n/a
Beaumont et al. 1991[24]	San Francisco FD	Cohort	SMR	84 (64-108)	99 (63-147)	145 (77-249)	57 (19-135)	68 (19-174)	81 (26-190)	95 (87-104)	75 (43-123)
Burnett et al. 1994[26]	27 U.S. States	Surveillance	PMR	102 (94-111)	n/a	148 (105-205)	99 (70-137)	144 (108-189)	103 (73-141)	101 (97-105)	83 (73-94)
California Dept. Health Svcs., 1987[27]	California, adjusted for smoking, alcohol, SES	Surveillance	SMR Adjusted	132 (89-190)	131 (48-284)	n/a	115 (24-337)	n/a	126 (99-158)	57 (7-206)	n/a
Demers, Heyer, Rosenstock, 1992	Pacific Northwest Municipal FDs	Cohort	IDR v. Police:	95 (67-133)	158 (73-343)	89 (30-266)	16 (2-124)	n/a	163 (70-379)	88 (74-104)	89 (47-169)
Dubrow and Wegman, 1984[28, 29]	Massachusetts firefighters, 1971-73	Surveillance	SMOR (on mortality)	86	76	60	110	122	86	n/a	n/a
Eliopulos et al 1984[30]	Western Australia. Wild fire fighters	Cohort	SMR	104 (42-213)	159 (43-407)	n/a	108 (29-276)	108 (29-276)	n/a	84 (60-114)	65 (13-190)
Feuer and Roseman, 1986[31]	New Jersey	Cohort	PMR, NJ state comparison	92	n/a	n/a	n/a	n/a	n/a	111	n/a
Giles et al., 1993[32]	Melbourne FD, Australia	Cohort	SIR	0.77 (0.28 – 1.68)	1.36 (0.62 – 2.59)	1.36 (0.62 – 2.59)	1.02 (0.28 – 1.68)	1.02 (0.28 – 1.68)	n/a	n/a	n/a
Guidotti, 1992[19]	Municipal firefighters, Alberta	Cohort	SMR	142 (91-211)	161 (88-271)	161 (88-271)	316 (86-808)	414 (166-853)	147 (30-429)	110 (92-131)	157 (79-281)
Guralnick, 1963[33]	U.S. census, 1950	Surveillance	SMR to 65y	83	93	93	n/a	n/a	n/a	72	n/a
Hansen, 1990[34]	Danish census	Cohort from census sample	SMR, v. civil servants	163 (75-310)	n/a	n/a	n/a	n/a	n/a	115 (74-171)	n/a

Table 1. Selected Cancer Risk Estimates from Major Studies of Firefighters.

AUTHORS, YEAR	POPULATION	DESIGN	RISK ESTIMATE	LUNG	COLON	RECTUM	BLADDER	KIDNEY	BRAIN	CVD	COPD
Heyer et al. 1990[35]	Seattle FD	Cohort	SMR	97 (65-139)	79 (32-164)	65 8-237)	n/a	n/a	95 (20-279)	75 (63-89)	n/a
Lindsey et a., 1993[36, 37]	Canadian labour force sample	Cohort from census sample	SMR v. employed	111 (41-242)	154 (19-556)	n/a	n/a	n/a	0 (0-625)	n/a	n/a
Ma et al., 1998[38] (white)	24 US states	Surveillance	MOR	1.1 (1.0 – 1.2)	1.0 (0.9 – 0.2)	1.1 (0.8 – 1.6)	1.2 (0.9 – 1.6)	1.3 (1.0 – 1.7)	1.0 (0.8 – 1.4)	n/a	n/a
Ma et al., 1998[38] (African-American)	24 US states	Surveillance	MOR	0.8 (0.5 – 1.3)	2.1 (1.1 – 4.0)	0	1.2 (0.9 – 1.6)	1.3 (1.0 – 1.7)	1.0 (0.8 – 1.4)	n/a	n/a
Ma et al., 2005[39]	Florida certification registry	Cohort	SIR	0.65 (0.54 – 0.78)	1.16 (0.92 – 1.45)	0.88 (0.56 – 1.32)	1.29 (1.01 – 1.62)	0.78 (0.52 – 1.14)	0.58 (0.31 – 0.97)	n/a	n/a
Mastromat-teo, 1959[40]	Toronto FD	Cohort	SMR	n/a	n/a	n/a	n/a	n/a	n/a	[141]	n/a
Massachu-setts Dept. of Public Health, 1990[41]	Massachusetts resident firefighters	Surveillance (incidence)	SMOR State:	122 (87-169)	120 (80-182)	145 (84-219)	159 (102-250)	n/a	86 (34-215)	n/a	n/a
Milham, 1983[42]	Washington state residents	Surveillance	PMR	105	90	103	233	115	194	116	53
Musk et al. 1978[43]	Boston FD	Cohort	SMR	88	n/a	n/a	92	103	86	n/a	n/a
Petersen and Milham, 1977[27]	California state residents	Surveillance	PMR	168	113	48	82	175	90	108	[70]
Rosenstock et al, 1990[44]	Pacific Northwest	Cohort	SMR v. US:	134 (90-191)	95 (41-187)	119 (44-259)	23 (3-83)	27 (3-87)	210 (131-317)	82 (74-90)	119 (72-183)
Sama et al., 1990[45]	Massachusetts cancer registry	Surveillance	SMOR v police	130 (84-203)	104 (59-182)	97 (50-188)	211 (107-414)	n/a	152 (39-592)	n/a	n/a
Tornling et al., 1990[46]	Stockholm FD	Cohort	SMR	90 (53-142)	85 (31-185)	207 (89-408)	31 (1-170)	110 (30-281)	279 (91-651)	98 (81-117)	0 (0-48)
Vena and Fiedler, 1987[47]	Buffalo FC	Cohort	SMR	94 (62-136)	183 (105-297)	208 (83-428)	286 (130-540)	130 (26-380)	236 (86-513)	92 (81-104)	n/a

Measuring Risk

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 approaches 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 this 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) and when referring to the fraction of all deaths represented by the particular outcome it is called the proportionate mortality ratio (PMR). (Confusingly, some authors, such as Baris et al.[18] express SMRs as relative risks without the conventional normalization to 100.)

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.

In this report, risk estimates will be presented as they were reported in the original paper. SMRs are either given to three figures, without decimals, or expressed as relative risks as in Baris et al.[18] Relative risks are given as decimals, with no qualification. Odds ratios identified as such and are given as decimals.

One 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. In epidemiology, and statistics, "rare" is a term of art meaning that the outcome of concern is very uncommon relative to all outcomes, and so 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.

Doubling is important for another reason.[48] An RR of 2.00 corresponds to "even odds" (OR = 2.0) meaning that the outcome had an equal probability of being associated with one cause of interest or with all other causes, taken together. In effect, it is the statistical representation of the "balance of probabilities" for one cause or another. RR = 2.0 or OR = 2.0 means that the risk attributable to conditions of work is at least equal to the risk for the general population and represents a high degree of association. It means that the attributable risk due to work is at least equal to the shared risk from other factors in life, including environmental factors associated with living as a member of the community. Applied to firefighters pursuing a claim in a workers' compensation system, a RR of 2 implies that, all other things being equal, the risk of a

firefighter developing a cancer (such as bladder) from work-related exposure is approximately equal to that of the risk of the same cancer in everyday life. Therefore, it is a statistical expression of the standard that it is "more likely than not" that the condition arose out of work. This constitutes the basis for a presumption, under which all such cases arising in workers in a particular occupation would normally be considered work-related unless there is evidence to the contrary or an alternative cause of greater certainty in the individual case. [5, 49 12, 48]

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. A more useful way to express this 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.[ùù] 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. Box 1 shows in an accessible and simple way how the ARF relates conceptually to apportionment.

Box 1. The difference between attribution and apportionment.

"Attribution" is an epidemiological term, applicable to populations, not a workers' compensation term. The workers' compensation analogue is "apportionment", which applies only to the proportionate influence of risk factors in an individual case.

Attribution is an estimate of how much or in what proportion a risk factor (which may itself be a cause or a marker that reflects the action of a cause) accounts for the total number of cases of the disease in question. Attribution can be expressed as the number of cases (attributable risk) or the proportion of cases (ARF), usually the latter, and reflects the distribution and contribution of risks in a population. Apportionment refers to the estimation of the contribution of a cause to the outcome in an individual, such as a claimant for compensation. The two concepts are frequently confused. 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.

The difference between attribution and apportionment can be illustrated by an accessible example. In a population of unusually hapless people living in a village in an unusually dangerous forest, there is elevated mortality in the vital statistics category of death by predation, which may be attributed by the following ARFs: 51% to being eaten by bears, 30% to being eaten by wolves, 15% to being eaten by cougars and 4% to being chewed to death by wolverines. That does not mean that in the individual case, slightly more than half of the corpse was eaten by a bear, the leg by wolves, the arm by a cougar and the remaining bits by wolverines. It means that in the absence of any further information, any remains found in the forest are more likely to have been the consequence of an encounter with a bear than with any other predator, or with all other predator types combined. Even so, other causes of death would have been possible and the risk of these alternatives would have been substantial, regardless of the actual predator that caused the demise of the villager. A combination coroner and game warden assessing cause of death without benefit of other knowledge (such as animal tooth forensics) would be right most of the time but wrong some of the time by always attributing the death to a bear; he or she (coroner-game wardens are presumed to be either gender) would be wrong most of the time but right some of the time by always attributing the death to a wolf or a cougar. The problem is that without further evidence he or she would not know which cases were right and which were wrong. On the other hand, he or she would be wrong almost all of the time assigning responsibility to wolverines and right so rarely that it would be an exceptional case requiring positive evidence to be accepted. In fact, the first case of death by wolverine would probably be missed entirely because there would be no experience with it. Note also that when ARFs from multiple studies are added up, their combined ARFs almost always add up to more than 100%. This is typical of the findings of epidemiological studies and reflects the common finding, most obvious in cancer and cardiovascular disease, that more than one cause may operate at the same time. The wolverine may bite the survivor of a bear attack.

Presumption

Presumption is, simply, the policy that claims should be accepted without opposition when, all other things being equal, a claim received from a worker in a certain occupation is demonstrably more likely than not to have arisen out of work, whether or not it is possible to prove the association in the individual case. A presumption assumes that, all other things being equal, most cases of a certain type are associated with occupational exposure, even though it is not possible to determine which.[12]

Presumptions are normally rebuttable, meaning that the adjudicating body may also examine evidence in the individual case that supports or calls into question the individual claimant's risk and the relationship to work. For example, a strong family history of the disease, the presence of a strong personal risk factor (usually smoking) or a work history that is incompatible with latency would all be grounds for rebuttal. Presumption is a way of being inclusive in the acceptance of such claims given that it is not possible to distinguish among them.

Presumption is a means of achieving consistency, administrative efficiency and fairness in the management of claims. Claimants must generally demonstrate that they belong to the group and satisfy certain criteria such as duration of employment and latency. Rebuttal criteria must be addressed with evidence or convincing argument. In the end, it is still the merit of the individual case that matters but the presumption facilitates adjudication.

Contrary to assumption, the adoption of presumptions does not really substitute a policy-derived formula for individual evaluation. Epidemiology contributes to the weight of evidence on general causation but in the workers' compensation system all claims must be decided on their individual own merits, as required by their acts. The use of presumptions and population risks are intended to provide guidance and only an estimate where the individual risk cannot be known. Epidemiology provides a meaningful and fair estimate of risk for the individual when the individual risk cannot be known and relieves the claimant of the considerable and often impossible burden to prove the unknowable. Population attributable risks are acceptable as crude estimates of individual risk, serving as best estimates when there is no specific information on which to estimate individual risk and are commonly used for this purpose in medicine, forensics, and compensation. However, when there is information specific to the individual, it should be used and most Acts require attention to the individual case.

A presumption assumes that, all other things being equal, most cases of a certain type among workers in a given occupation are associated with occupational exposure, even though it is not possible to determine which among the individual cases. The face validity of a presumption is therefore clearest when the risk for the group is at least doubled compared to a relevant reference population. A RR of 2.0 or an SMR of 200 is equal to an attributable risk of

100% of expected, or an attributable risk fraction of 50%, and represents a high degree of association. It implies that the attributable risk due to work as a firefighter is equal to the shared risk from other factors in life, including environmental factors associated with living as a member of the community. As a practical matter, in workers' compensation and tort litigation an SMR of 200 implies that, all other things being equal, the risk to a firefighter of developing a cancer (such as bladder) from work-related exposure is approximately equal to that of the risk of the same cancer in everyday life. Therefore, the proposition that the cancer arose from work and that it did not are equally likely, have equal odds and it is as or "more likely than not" (giving the benefit of the doubt to the worker) that the condition arose out of work. This constitutes

the basis for a "rebuttable presumption" under which such cases would normally be considered work-related unless there is evidence to the contrary.[5 51]

Presumption is usually based on the demonstration that the relative risk exceeds two because this statistical measure corresponds to even odds, but in practice, it is impossible to make such a fine distinction. A relative risk of 1.7 or 1.8 (SMR of 170 or 180) is usually indistinguishable statistically from one of 2 (200) with any confidence, at least for rare outcomes. Presumption is most appropriate when the condition is rare and there is a pattern or strong suggestion of strong association with an occupation that may be concealed by other factors that complicate interpretation of the risk estimate.[4, 5, 10, 52]

It would be desirable from a scientific basis to establish the subgroups in which the risk is concentrated, to identify the specific types of cancer in the aggregate categories most likely to be associated with elevated risk and to determine the threshold level associated with significant risk. However, to do so is not feasible, any more than it is now practical to identify the specific carcinogen that is responsible for many risks.

In the real world, there will be errors of inclusion, in which claims are accepted that are not actually arise from occupation, and errors of exclusion, in which claims are rejected for diseases that actually did. How many depends on the risk ratio and attributable risk fraction. If all claimants are awarded, and if the RR = 2.0, then approximately 50% of cases will have been given compensation when the disorder did not arise from work, but which cases these are cannot be known. If the RR = 4.0, then approximately 25% of cases will have been given compensation when the disorder did not arise from work, but which cases cannot be known. The only ways to minimize the potential for error are to make the criteria as solidly based on the (preponderance of) evidence as possible, to review the criteria frequently in light of new knowledge (which may have the unintended consequence of leading to inconsistency of claim decisions over time), and to eliminate bias in the process.

To reject all such claims or to apply criteria that are arbitrary, such as restricting compensation to non-smokers, would predictably deny benefits to persons whose disorders did in fact arise from occupation but who cannot demonstrate the association, often due to limitations in the available knowledge (as noted earlier). To accept all such claims would predictably include all such cases in which the disorder did arise from work and also those that did not arise from occupation, with no opportunity to rebut non-meritorious claims. A policy that applies arbitrary additional criteria, such as restricting compensation to non-smokers, will inevitably deny benefits to some, usually many, claimants whose disorders did, in fact, arise from work but who cannot demonstrate the association conclusively. To apply criteria that are liberal, i.e. that include almost all workers with a plausible claim and exclude those who do not fit the criteria, inevitably raises issues regarding the adequacy, specificity and validity of the criteria and is likely to exclude some few individuals whose condition did arise out of work but may not have fit the inexact criteria precisely. To avoid this problem, liberal presumption is sometimes applied as a means of ensuring that as many as possible of those persons whose disorder did arise from their occupation are compensated, recognizing a social benefit to fair compensation of most of those whose condition did arise from work over the cost of inevitably accepting some claims in which it did not, but offsetting this cost to some degree by minimizing operational expense.

Aside from equity and social benefit, presumptions also have other positive features. They are administratively simpler to manage than disputed claims and recognize special situations, such

as the risk assumed voluntarily by public safety personnel. They remove a huge burden from the claimant and this tends to reduce the cost of applying for claims and the need for lawyers.

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). True latency is rarely knowable, because the action of the cause cannot usually be pinpointed.

Latency in cancer epidemiology is the elapsed time between first exposure to a carcinogen and the clinical manifestation of the disease. 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 as the 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.

Positive and Negative Findings

An epidemiological approach based on a standard of “more likely than not” accepts 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.

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.

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, because it is not common enough, although it is one of the most common cancers and since 1987 the most common cause of cancer deaths for both men and women.[53] This means that a large fraction of studies without question miss the true association. This is not controversial: it is inherent in the definition of power, as well as easily observed in practical experience.

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 which 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 may 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 unity, are usually, and often wrongly, taken at face value in practice. However, in the situation of low power for a rare outcome, they may 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. Trends over time may obviate the relevance of earlier studies in calculating current risk, if only because of differences in exposure profile and interaction with smoking habits, and the underlying populations will differ.[2]

As a scientific problem, such discrepancies are often considered, and are always described in the literature, as a challenge for further investigation However, replication is not likely to resolve many practically important questions or clarify the risk for the least common "rare" diseases such as the individual lymphomas and leukemias, especially given priorities of major funding agencies such as the National Institutes of Health (US). (The Canadian Institutes for Health Research funds few studies in which occupation is the major focus.) The National Institute for Occupational Safety and Health (US) is conducting its own multi-center investigation of firefighters, the results of which should be available in several years; it is currently still in the planning stage. It is unlikely that for all but a handful of occupations, particularly for firefighters, fundamental questions about the accuracy of the risk estimate will be resolved before the occupation itself changes due to technology or economic trends and the question becomes

irrelevant to new workers. Adjudication of 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.

The argument begins with a close examination of the meaning of "power". Power is the probability that a finding, in this case an elevated risk that is truly present in an exposed population will be observed in a particular study. Its formal expression is $(1 - \beta)$, where β is the probability of making a Type II error, in which a finding that should have been detected because it is present in the population under study is missed, not detected. As in most science, greater attention is given to preventing a Type I error (the probability for which is α), in which a finding that is not actually present in the population is mistakenly reported. This represents a value judgment that it is better to be wrong by omission than to assert something that is false.

The logic behind the assumption that α should be greater than β dates to the early years of statistical inference and has deep roots. Its practical root lies with the idea that for the advancement of science, it was preferable to avoid introducing false conclusions but that, science being a systematic and self-correcting enterprise, missing a finding that truly present was less serious because science would eventually find it. The philosophical root came from Karl Popper, whose doctrine that science advances only through "falsification" and called for a clear statement of the proposition to be disproven. Since it is not possible to falsify the absence of something, the α value, and consequently power, was set with a high bar for falsification, but the β value was set to be a lower bar for acceptance because it was deemed more acceptable to miss a finding than to mislead scientists into believing something that is not true.

By convention, the value of α is set to allow no more than one error in twenty replicate studies, or 0.05. However, the value of β is always much higher, commonly 0.2, for a power of 0.8 for the

main effect under study. This means that there is one chance in five of concluding that there is no finding when one actually exists. The minimum acceptable power, 1 – β, in conventional studies designed to search for (more accurately, to falsify the search for) a particular effect is about 0.8, for an 80% chance of detecting the effect if it is present (effect size being specified in the study design). If these studies do achieve a power of 0.8 for cancers, it is usually only for total cancers, which is rarely useful as a practical matter. These conventions work well for common diseases such as cardiovascular diseases when the study is designed to have sufficient power for one or a small number of important and common outcomes

Unfortunately, these same conventions work poorly in practice for rare outcomes such as many cancers, which are usually studied in aggregated groups (such as brain, or lymphoma, or leukemia) in any single, limited cohort or case-referent study. In practice, a cohort study, particularly in this literature, usually examines 20 or 30 outcomes together and the power of a study to identify the true risk of a rare conditions is seldom much more than 0.1 and usually less, much less for many rare diseases such as the individual lymphomas. Looked at another way, this means that fully 90% or all studies in the world literature are likely to miss the association.

Studies that identify some effect but "miss" an accurate estimate of the risk will more often profoundly underestimate the risk than overestimate it, because statistical error is not distributed evenly at extremes of frequency. When one expresses the probability of finding a given result in terms of power, one is saying that the probability of identifying all values above the critical effect size is greater than that power. This means that the studies that greatly underestimate the risk are part of the prediction from β. The few studies that overestimate the risk fall into the probability space of the much smaller 1- β. This also means that there is a distribution around the critical effect size in the area of the curve of interest, which logically would be asymmetric because underestimates are more common than overestimates. This means that there is a distribution around the critical effect size in the area of the curve of interest, which logically would be asymmetric. This makes sense because underestimates are more common than overestimates. Extreme high risk estimates are less likely than risk estimates closer to unity, due to chance alone.

All investigators are accustomed to calculating and interpreting the value of α across a wide range of values. However, in studies designed for common outcomes, (1 – β) is set in advance for the main effect. For rare diseases that are incidental to and not the main objective of studies, which is almost always the case for individual cancers in the universe of firefighters studies, in practice (1 – β) for other outcomes is calculated after the fact. Few investigators are much concerned with the power to detect rare outcomes unless the study has shown a "positive result." At that point, findings are typically examined in retrospect, in order to evaluate whether they are likely to be "true" findings. The effect size is usually expressed as a relative risk in most occupational cancer studies.

The difference in value placed on avoiding the two errors may have resulted in a logical fallacy creeping into practice, as follows.

Power answers the question, is the study more likely to find what was there or is it more likely to miss it? For any study with a low power for a particular finding, the answer is that the study will probably miss it. Therefore for rare outcomes, power predicts that the effects observed in most studies will cluster around unity with random error, showing a more or less normal distribution. In other words, there is a subset of studies that will have missed the effect entirely, not just

underestimated it, and data from these studies will carry no information. There will not even be information that can be used as the denominator for a rate, because power is a function of one sample derived from one population, not one sample from one population pooled with another subpopulation from a study that has missed the effect.

A much smaller subset of studies will show the effect, when power is low. Regardless of power, the actual value of a risk in a population is the most likely value for the point estimate of that risk for studies that detect the effect, more likely than any other value in positive studies. This means that in the subset of studies that are "positive", there will also be a distribution of point estimate values around the true value. This distribution will be asymmetric and more dense on the left (closer to unity), both because the power curve is asymmetric (it is asymptotic above the threshold effect size) and because extreme values are less likely than values closer to unity or the true value.

Consider a situation in which a large set of identical replicate cohort studies have been performed, using identical methodology and performed on the same population. They all have a uniform power of 0.2, which in practice is unrealistically high for rare outcomes. The threshold effect size is a doubling of risk, chosen because it is an important benchmark for medicolegal purposes, because it corresponds to "the weight of evidence" or "more likely than not" when an occupational group is compared to the referent or general population. Clearly 80% of those studies will, predictably, be "negative", in that they will not show an elevated risk, not because it is not there but because they simply missed it. Among those "negative" studies, there will be a normal distribution of values around unity (no elevation in risk). However, 20% of those studies will, predictably, be "positive", in that they will show an elevated relative risk, greater than or equal to 2.0. There will also be a distribution of risk estimates in those studies but it will be centred around 2, and somewhat skewed to the left (i.e., the curve is not Gaussian (bell-shaped), although it may be in a logarithmic transformation). Therefore, even under these highly artificial assumptions which favor detection of an effect in a rare disease, the result is approximately what one typically finds in the firefighting literature for selected cancers of interest, namely a subset of studies clustered around unity and another subset more or less clustered around a higher risk estimate.

In this thought experiment, the most common value for the elevated risk will be close to the true value in the sample for the "positive" study, but not for all samples from the population. If the number of studies showing the effect is plotted against the effect size, there will be two modes. the largest mode will be "negative", but entirely "wrong" in describing the true risk in that population. The estimate cannot be improved upon by pooling results from studies that missed the effect, and therefore carry no information, with studies that captured it and that carry all the information, because doing that will only dilute the more accurate estimate from the studies that captured it.

Now, one may imagine that instead of many replicate studies there are only 10, but they follow the same statistical pattern. That would mean that two positive studies showing a true effect will be compared with eight studies that missed or greatly underestimated the effect. This would normally be considered "conflicting results" in the literature, with the weight of evidence favoring the negative result. A meta-analysis would probably be undertaken, with the result that the risk estimate would then be diluted by the inclusion of essentially null findings from four studies that missed the result for every one that carried a valid result. The diluted risk estimate would most likely be dismissed as "negative" overall. This interpretation would be completely mistaken, however.

Because power is based on the probably of finding a true result, it should be obvious that some studies that do not show an excess risk are negative simply because they missed the true result. On the other hand, a "positive" study is more likely to be a valid result that captures the true result. It follows that inconsistent results should be interpreted with care but not unduly conservatively. Compounding this problem is the general tendency of common sources of bias to result in underestimates of risk, principally through misclassification.

In many relevant outcomes for firefighters, such as cancer of the brain, there is clearly a mode at RR = 1.0 (no risk) and a second mode around an elevated risk, with a distribution on either side, with not much in between. This suggests that although it may be obscured by dilution through aggregation and the "grainy" nature of data where there are relatively small numbers involved, the curve follows what would be predicted for a true effect in studies with low power. The pattern can be seen in several other cancers in firefighting populations.

The first implication of this analysis is that practical decisions, especially where matters of equity are concerned, should 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.

The second implication is that meta-analysis may systematically underestimate the true risk when studies of low power are aggregated, because studies that 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.

Studies of firefighters are generally in conformity with these assumptions and conform to these implications, although all studies are not identical.

Meta-analysis

Meta-analysis has become popular in part in an effort to get around this impasse and particularly to get around the limitation of power.[54] Meta-analysis cannot improve the underestimate of risk that normally accompanies misclassification by raising the number of subjects but it may make a Type II error less likely. Meta-analysis may provide useful guidance, especially for more common diagnoses such as myocardial infarction, but its use has been disappointing and even misleading applied to studies of firefighters. For example, early meta-analyses[55] did not predict or anticipate the subsequent pattern of firefighter-related cancers in other meta-analyses[56, 57] or with any better or with more precision than reading and interpreting the individual papers[5, 58], as will be shown.

Although meta-analysis has not performed ideally even in the much more favourable setting of multiple drug studies in which their outcome is compared to that of definitive clinical trials, it is one statistical approach that can be used when the underlying population is relatively uniform and the study methods are very similar. Firefighter studies come closer to meeting this ideal than those of most occupations but it is not correct to think that all firefighter populations are alike, that the communities from which they come share identical background risks, that different eras presented the same set of risks, that the opportunity for exposure is the same random distribution in each fire department, or that exposure is different in cities with different stocks

of housing and commercial buildings. Firefighter studies are similar by no means identical.

Meta-analysis does not address these issues effectively and is, at best, a crude statistical tool useful for guidance at the most general level but probably too crude for general causation. In epidemiology, a reevaluation of meta-analysis is occurring because of its conspicuous failures in predicting the result of clinical trials, for which it would seem to be ideally suited.[54]

Past efforts at meta-analysis also did not successfully identify several cancers for which later cohort studies provided strong evidence for a probable increased risk, such as kidney and bladder.[55, 57] Pooled studies with large populations but limited resolution have not fully resolved these issues, either.[59, 60] A meta-analysis, analyzed in the literal definition of power, is not likely to be very helpful in the case of a rare disease because the true risk will merely be diluted by the low risk estimates of studies that failed to detect the (true) elevation. The reasons are outlined in detail below.

The central tendency of studies on firefighters does appear to show an excess risk for many outcomes, specifically a small group of uncommon cancers, and the meta-analysis shows this. However, as in most meta-analyses, the magnitude of the risk estimate is probably underestimated. Power considerations predictably result in a substantial number of studies showing "negative" results for "rare" (meaning infrequent and unlikely to affect the total, overall risk estimate) diseases. These negative studies are not as useful as positive studies in estimating the true risk, both because those studies that miss the risk because of power considerations carry no inherently useful information (because, after all, they missed it) and because the biases (classically misclassification bias) and limitations of epidemiological method generally result in underestimate and a diluted risk estimate rather than an overestimate. The weighting factors in meta-analysis help, incompletely, to account for the power problem but they cannot deal with the issues of study bias or with publication bias.

There is no substitute for looking at the data in individual studies, weighing their strengths and weaknesses, and to the maximum extent possible determining the trend of the data within well-designed studies, accounting for possible confounding and dilution.

Meta-analysis has been applied to the literature on firefighters and cancer, with mixed results in light of subsequent studies. The performance of meta-analysis in predicting that cancer risk would be identified in the future by investigators applying appropriate study designs and widely accepted has been poor, based on past studies.[61] The method confirmed elevations for some cancers (brain and myeloma) that were already recognized at the time but did not address the issues that have been raised in this paper and missed associations which are now widely accepted. Pooled studies with large populations have not fully resolved these issues, either.[59] The most recent major meta-analysis of firefighters[59, 62] applied a rather rigid set of arbitrary validation criteria to the findings after the initial analysis, culminating in exclusion of some associations on questionable grounds that biased the outcome against plausible firefighting-related cancers. For these reasons, meta-analysis is used only tentatively and not as an organizing principle in this report.

Evaluation of associations between occupation as a firefighter and rare diseases presents a class of problem in occupational epidemiology that is better approached rigorously by examining the structure of the problem outcome by outcome.[5] As argued elsewhere in this report and in the professional literature[5], an alternative approach to addressing this problem is to take into

account the totality of the evidence.[63] The summary estimate of overall SMRs of published studies should not be considered to be determinative. Conventional (let alone "quick and dirty") meta-analysis based on such summary risk estimates is frankly not very useful, especially applied to an individual case.

A corollary is that other statistical approaches may be more valuable than tallying up positive studies against negative and seeing which list is longer or performing a meta-analysis which mixes studies, weighted or otherwise, that missed the effect with those that captured it. Such approaches may include testing for evidence for a bimodal distribution, rather than the treating the outcomes of each study as if they were a snapshot or microcosm of the whole population which can be reassembled through meta-analysis. In practice, this is never done.

The "Hill" Criteria

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). They were proposed by British biostatistician Sir Austin Bradford Hill (1965) in a lecture, during which he emphasized, without equivocation, that his criteria were guidelines, not rules and were neither infallible nor proof of causation.[64] The Hill criteria apply only to populations, never individuals, and only when there are sufficient epidemiological studies available to make broad generalizations. Since studies on firefighters are relatively numerous, some authors have been tempted to apply the Hill criteria to various associations of firefighting.[65]

Science advances by not being able to disprove (falsify) a hypothesis, not by compiling evidence in favour of one. The methods of epidemiology are capable of ruling out a causal effect but alone they are not able to establish causation with certainty. For this, additional studies are needed using the methods of toxicology and experimental biology. Thus the powerful but one-sided blade of epidemiology cuts just one way, to falsify.[12]

The central question in most environmental or 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 and so this dimension adds a further layer of complexity to any issue in environmental and occupational health that matters.

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. 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 this is not such a trivial association: that 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 the prevention of smoking.

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. Hill proposed these criteria as a guide to confidence, not as standards for proof. He was perfectly clear that these criteria were a provisional test, not definitive proof. The more criteria that are satisfied, the more *likely* it is that the association observed is truly causal. Some criteria are stronger than others. These criteria are presented in Table 2.[66]

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 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, which 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, if the exposure is to 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, 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.

Analytical Frameworks

A common problem in epidemiology is “paradigm blindness”, which occurs when attention to study design and accounting for confounding and bias distracts the investigator from the realization that the construct of the study does not model reality. It is most common when an approach to study a problem seems obvious but the question being asked or the analytical strategy makes little or no sense in practical terms.

Paradigm blindness often arises because of limitations on the information available to epidemiologists. There are two closely related problems that are obvious in the literature on firefighters: inappropriate aggregation of biologically distinct outcomes and dilution of risk estimates.

Inappropriate aggregation occurs when similar but distinct outcomes, such as related cancers or cancers that occur at a common site, are aggregated for analysis. The standard approach taken by occupational epidemiologists is to aggregate cancers at a particular site or of a certain broad classification. For example, it has been customary in the past to examine disease risk for leukaemia, lymphoma, and myeloma together, not as separate disorders. This is partly because death certificates do not provide sufficiently detailed information to categorize them further but also because it is perceived as necessary to accumulate sufficient numbers on which to perform the analysis and this cannot be done if the category is split more and more finely because the numbers get smaller and the power grows much weaker. Medically, however, the result is meaningless because leukaemia, lymphoma, and myeloma are not only distinct from one another but in themselves are broad disease categories, each covering dozens of individual diseases with highly variable characteristics and, when known, different known etiologies. For

example, only one type of leukemia is known with scientific certainty to be associated with benzene, acute myeloid (myelogenous) leukemia (which itself has three main types), which is also induced by ionizing radiation. It happens to be the second most common form of leukemia in adults, but chronic lymphocytic leukemia is more common and there are several others (the classification system is constantly being refined). In a hypothetical population in which the distribution is 40% chronic lymphocytic leukemia (CLL), 20% acute myelogenous leukemia (AML), and 40% other, and the threshold for recognizing an elevation as significant is a relative risk of 1.5, there would have to be a relative risk of 3.5 for AML to achieve that threshold for all leukemias taken together. If in the same population lymphomas are twice as common and myelomas roughly half as common as all leukemias combined, then AML would have to be elevated about 6.5 times for the excess to be evident. Obviously these very high elevations would also be uncertain, given the statistical problems introduced by insufficient power. The final result is that the significance of what would appear to be a low elevation in the rubric overall would be lost: the "signal" for an increased risk of an exposure-related leukemia would almost certainly be missed in studies that aggregated these outcomes without looking at individual diseases.

Another way to look at this problem is by analogy. Box 2 presents an illustration of how this problem, using a hypothetical example completely unrelated to firefighters, in order to distance the explanation from firefighters and in so doing introduce further objectivity.

Box 2. An Illustration of the Program of Aggregation and Dilution

Suppose you were asked to comment on causation in the case of a woman who developed a cancer unique to women. However, you live in a world in which epidemiology is very rudimentary. Your only information is that someone told you that the risk of developing "female cancer" for every adult Canadian, including residents of Québec, is (approximately) 74.5 per 100,000 per year.

If you were paying attention, your first reaction would be: "that makes no sense!" First of all, somewhat less than half of all adult Canadians are men, who rarely get "female cancer". (To complicate matters even more – some do, specifically male breast cancer, but this is rare.)

Then, you would ask the person for their definition of "female cancer". You would learn that the category of "female cancer" used by your informant mixed up breast, ovarian, cervical and uterine cancer indiscriminately. However, you (although perhaps not the bureau that provided you with these statistics) know perfectly well that the risk factors for all of these cancer types are different, although there is some overlap. So you would want the data broken out in the study results.

Suppose this information were not available. You would then want to know at least which types of cancer were most common and have some idea of their relative frequency. You would soon learn that breast is much more common than the other three combined: you would therefore conclude that cancer rates for this one type were probably driving the statistically calculated rates for the entire category of "female cancer". Then you would still have to figure out the risk for an individual at a certain age and that individual's personal and family history, since breast cancer risk varies considerably by age and biological risk factors.

If you were actually able to get to the true incidence figures – in other words, if you were able to go beyond the report you were given to something approximating truth – you would quickly find that the incidence for adult women in Canada per 100,000 is (approximately) 107 for breast, 19 for uterus, 15 for ovary and 8 for cervix. But you do not have these figures. Nobody has them in this naïve epidemiological universe.

You would have another problem. If the risk of cervical cancer doubled or even tripled, it would still be only a blip in the overall rate of "female cancer". You might not even notice such a difference, considering that there is random variation from year to year and considering that the rate of cervical cancer is decreasing slowly and the rate of (detected) breast cancer is increasing, but faster. In other words, an increased risk would not only be diluted but could easily be buried by countervailing trends headed in opposite directions.

If you then made recommendations for the prevention of "female cancer" based on what you knew, your recommendations would not only be wrong, but dangerous. That is because your conclusions would most likely be based on risk factors for breast cancer, because it overwhelms the category of "female cancer" and the risk factors for other cancer types would not show up clearly, or even at all. That, in turn, would be highly dangerous for public health because cervical cancer has specific risk factors than can be effectively managed (for example, by screening, HPV vaccine, and health education) and recommendations based on breast cancer would be completely ineffective in preventing it.

Now, what if there were a question involving eligibility for compensation. If you just took the risk estimate at face value and applied it to an individual in order to make a conclusion about causation, you would be doing a grave disservice to the woman who has developed the cancer. Your conclusions would again most likely be based on risk factors for breast cancer and if the woman had cervical cancer your conclusions would be all wrong. You would have to dig deeper to get a closer, but admittedly imperfect, approximation to what was really going on.

This is something like the problem we face with firefighters, with greater variability in the statistical data. Diseases that are biologically quite different are lumped together in categories that have to be disentangled. Smokers and nonsmokers are all mixed up. Different lengths of service and other indicators of exposure are not consistently reported. Therefore, we have to make sense out of it by examining the evidence in light of what we know, not by blindly following statistical conventions.

APPROPRIATE METHODOLOGY.

We suggest that these issues 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.[12]

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.[10] 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 at least a doubling 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.
- Modelling for lung cancer among nonsmokers and for other cancers by whether the risk estimate increased in the study.
- 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.

THE WORK OF FIREFIGHTING

Municipal firefighters are the focus 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)
- wildfire (forest fire and brush fire) firefighters.

Municipal firefighters have received the most attention scientifically and are presumed to be the major group of interest to the WSIB as reflected in this RFP. However, wildfires and the firefighters that suppress them are important to the public safety and economy of Québec, especially in rural and remote areas. Only municipal firefighters will be covered in this report.

FIREFIGHTING ACTIVITIES

In order to understand the terminology used in this report and the issues involving exposure, it is useful to know some basics of how firefighters do their work.[67, 68]

Urban fires require tight containment to prevent spread to adjacent structures. The basic strategy is to keep the fire confined on the property and to the structure and to shrink the size of the fire. This is done by depriving the fire of fuel, by depriving it of oxygen, and by cooling the materials in the fire to below ignition temperature.

As a fire develops heat, it drives off flammable gases from the unburned material around it. These gases then catch fire when they reach the fire itself or another ignition source and the fire spreads or, if limited, is perpetuated. When there is insufficient oxygen or the temperature is not high enough, these gases accumulate and may feed a fire above them as they rise. When oxygen is abundant and the temperature is high or there is an ignition source, they are combusted and burn in flames or explode. The goal of "fire suppression", once the fire is prevented from spreading, is to prevent these flammable breakdown products of heat (a process called "pyrolysis") from catching fire, deprive the fire of oxygen (which has the effect of generating carbon monoxide), and to cool the fire to prevent spontaneous combustion and reduce generation of flammable gases.

"Knockdown", the colloquial term for fire suppression, is the phase of firefighting in which the flames are extinguished, pyrolysis is reduced, and the fire is brought under control. Water is laid onto the fire from the highest possible point to contain the spread of the fire and to cool the fire at its hottest point. This is usually accomplished by dispatching at least two pumpers to lay water on the fire, from the front and rear, as well as ladder trucks to allow firefighters to climb over the fire and to lay water on from above. As the fire is brought under control, it is extinguished from the periphery to the center. Another strategy is to cut or chop holes to ventilate smoke and to promote more rapid and complete combustion at the base of the fire in order to prevent combustible gases from rising and igniting at a higher point. When a space is filled with flammable gases driven out of the materials in the space by heat, there is a risk that they will ignite in a flashover, one of the most dangerous situations in firefighting.

Knockdown is associated with the potential for exposure to many products of combustion but in modern firefighting the primary hazard is physical safety and heat stress. This is because fire departments require, and have by now achieved firefighters' compliance with the requirement, for personal protection in the form of self-contained breathing apparatus (SCBA). SCBA is a tank of air carried on the back, with a face mask. For the duration of the air supply, 15 to 20 minutes, the firefighter is essentially protected against inhalation of smoke and toxic combustion products. However, higher temperatures also favor more complete combustion of organic material to carbon dioxide, resulting in generally less (but still significant) toxic chemical exposure, at least at height (toward the ceiling of a burning room, for example), which unfortunately is where the air temperature is hottest. At lower heights, (on the floor of a burning room) the temperatures are lower, oxygen has not yet been consumed, and toxic gases that are lighter than air are rising up and away.

SCBA gear is bulky and heavy. During knockdown the firefighter is weighed down by heavy turnout gear, which is even heavier when wet and which insulates the firefighter, both protecting him or her (there are few female firefighters) from external heat but also trapping internal heat generated by the body, especially during maximal exertion. SCBA gear adds to this burden and also changes the center of gravity of firefighters to a higher level and behind, making balance

more difficult during dangerous work often undertaken on uneven or unpredictable surfaces with limited visibility. There is a rule in firefighting that a firefighter must rest for 10 minutes for every 20 minutes that they wear SCBA during fire suppression in order to recover physiologically, but recent studies have shown that this is not enough long to maintain performance for long periods.[69]

Once fire suppression is complete, the structure must then be inspected to ensure that no burning embers are present that might restart the fire. This phase is called "overhaul" and it is associated with greater potential for exposure to toxic chemicals. The is due in part to the reduction in temperature of the fire, as it passes from a phase that promotes complete oxidation or organic compounds through a range where the chemistry favors formation of more toxic chemicals, such as polycyclic aromatic hydrocarbons and ultrafine particulate matter. The characteristic hazards of overhaul are also due to inhalation of partially-combusted gases, some of which are absorbed into concrete and released as it cools. Many firefighters, remove their respiratory protection at this point for better visibility and ease of movement on uneven ground. In the past, firefighters were known sometimes to smoke to relax after the exertion of a knockdown.

Because of the organization of modern firefighting, key tasks to which firefighters are assigned at the scene of a major structural fire are likely to include dragging hose, laying on water, ventilation (by breaking windows or chopping holes with an axe), climbing ladder, and rescue or salvage. Climbing the ladder with hose, especially using protective equipment, is exceptionally strenuous. The most strenuous exertion in firefighting, and universally the task considered most stressful, is rescue, when a person must be carried out of a burning building.

Wildfire firefighting carries different challenges. Fires in sparsely populated areas often involve brush, trees, or temporary structures. Here the emphasis is on containment in a broad area, cutting firebreaks to block the spread of a fire, setting backfires to burn off fuel in a controlled manner before the fire reaches a position, and preserving structures where possible. Forest fires are particularly dangerous under conditions of shifting wind and firefighters can be trapped if the effort is not well coordinated. SCBA cannot be used because firefighters must continue fire suppression for long periods of time while in place or moving on foot and because of the logistical problems of resupply and providing rest periods.

Fire services have placed increasing emphasis on prevention in recent years and on criminal investigation in suspected cases of arson. Training emphasizes realistic simulations with controlled fires, which present some of the same hazards as real fires. Arson investigation in a fresh fire scene presents hazards similar to overhaul.

WHY RESPONDERS TO THE WORLD TRADE CENTER DISASTER ARE DIFFERENT

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.[70]:

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[70]:

- 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 two academic-based programs (Mt. Sinai and New York University) each have maintained a comprehensive and elaborate monitoring program for WTC responders, and a third academically-based facility just opened (SUNY Downstate and SUNY Stony Book, in Brooklyn). 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.
- Strong evidence that FDNY members are indeed a separate and distinct cohort 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”. At least part of this excess may reflect the screening bias mentioned above.

Because of this evidence for distinct characteristics, WTC responders and municipal firefighters may of course be compared but not assumed to apply to all municipal firefighters.

WTC responders were exposed to the principal components of the dust on the first two days following the attacks of 11 September 2001 and to a much lesser degree thereafter, for several reasons. One was that the intense heat of the fires carried much of the dust and presumably most of the volatile toxic gases upward and away from street level and the collapsing buildings. Secondly, prevailing winds diluted and blew some of the plume eastward toward Brooklyn. Finally, a rain fell several days later and removed much of the remaining suspended particles in air. The most volatile hydrocarbons and gases that were lighter than air would have risen and dissipated quickly. Larger particles would have settled over a period of hours. (The dust observed in the air and on the street in news photographs would be the very largest particles, not those with the greatest potential for toxicity.) Very fine particles (including ultrafine particulate matter) may have stayed aloft for hours or days and so would not have settled, but concentrations would have fallen over time. Dust collected for later analysis in New York therefore consisted primarily of larger particles that settled within the first day and no volatile components could be measured. As a consequence, 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.

As best can be reconstructed, the primary exposure of WTC responders appears to have been to pulverized calcined calcium silicate derived from concrete, which was, as best can be reconstructed, relatively coarse (>10 Qm aerodynamic diameter) dust yielding a highly alkaline pH (> 8) in aqueous solution, together with an unknown quantity (because it was not measured) of ultrafine (which would have quickly dispersed anyway). 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 by a gaseous cloud of unknown composition which rapidly dissipated and which was replaced with focal sources of combustion products, 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 of this unusual profile of exposure, although some individual components, such as burning jet fuel, may be present in industrial firefighting on occasion. The effect of alkaline dusts on the respiratory tract has been little studied, except for trona miners, and the effects of a relatively insoluble and moderately alkaline dust on the respiratory tract is not known. (Trona dust is even more alkaline but is much more soluble than cement dust; trona causes intense mucosal irritation but not chronic lung disease.)

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.

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.[71] 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.[7, 72, 72-78]

EXPOSURES ENCOUNTERED DURING RESPONSE BUT NOT PRODUCED BY COMBUSTION CHEMISTRY	EXPOSURES PRIMARILY ASSOCIATED WITH COMBUSTION
Antimony (constituent of flame retardant on turn-out gear)	Acetaldehyde
Asbestos	Acrolein
Cadmium	Aldehydes (mixed)
Lead	Alkanes, straight chain (inc. propane*)
PFOA (perfluorooctanoic acid and its product polytetrafluoroethylene)	Alkenes, straight chain (inc. propene*, 1-butene*/2-methylpropene)
Pesticides	*Benzene**
Polybrominated biphenyl compounds (mixed, low)	Benzaldehyde
Polychlorinated biphenyl compounds (mixed)	Brominated hydrocarbons (low)
Silica dust	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*
	Heterocyclic PAH analogues
	Hydrogen chloride
	Hydrogen fluoride
	Hydrogen cyanide
	Hydrogen fluoride
	Isopropylbenzene
	Isovaleraldehyde
	Methylene chloride
	Naphthalene (a PAH)
	Nitriles (mixed)
	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 are more complicated in their toxic exposures than wildfires[30, 79], 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. In 1988, a fire in St. Basile-le-Grand involving oil contaminated with PCBs presented a special risk of exposure to these potentially carcinogenic chemicals and could have contaminated a widespread area of Québec, had levels been higher.

Firefighters are exposed to multiple chemicals, both at the same time and in rapid sequence, mostly by the respiratory route but somewhat by skin.[80] For specific health effects, the combination and the timing may be significant, but the complex interactions of these factors are poorly understood.

CARDIOVASCULAR DISEASE RISK

There has long been interest in the issue of cardiovascular disease risk among firefighters and an assumption that the risk is elevated. Baris et al., from 2001[18] (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, 95% CI = 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, 95% CI = 0.62-1.00). Feuer 1986 also showed an elevation for heart disease, with 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.[81] Other studies of firefighters have shown unremarkable risks for heart disease but most have also shown a relatively low risk for stroke.

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.[82] Unfortunately, this is demonstrably incorrect. It now appears, however, that the overall favorable mortality profile was concealing important anomalies.

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 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 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 83].

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.

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. Harvesting is not simply a matter of an inevitable event occurring early. For younger working people, these risks are not predestined, as they may seem to be for the elderly and infirm. The additional time to a cardiac event might be years, not just months and long enough to be concealed in mortality figures by competing causes of mortality. An event may then lead to years of active, productive and disability-free life lost, with implications for family security. 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 does occur, which would explain why overall lifetime mortality may not give a clear indication of occupational risk.

MORTALITY FROM CARDIOVASCULAR DISEASE

Against the high background of mortality from cardiovascular disease,[84] 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. Historically, however, studies have been inconsistent[85-88] and some have shown excess cardiovascular mortality confined to certain subgroups, such as firefighters aged 45 to 49[89].Much of the uncertainty has been resolved in recent years by a series of studies conducted by investigators at Harvard. There is now strong evidence that work-related activities may precipitate myocardial infarction in firefighters with pre-existing coronary artery disease.[90] 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[5, 68, 86, 91-94]:

- 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
- 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 (sympathic 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 64 (slightly beyond the usual retirement age of firefighters), which is 43.5%.[84, 91] 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[2, 5, 95] despite assumptions to the contrary[86, 92]. 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. (MMWR, 2006) However, most studies of American firefighters demonstrate an overall mortality risk for cardiovascular or ischemic heart disease close to that of the general population.[59, 62, 85] (Beaumont[96] 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, 95% CI = 0.35-0.75) compared to the general male population of France.[97] Likewise, Swedish urban firefighters showed the expected healthy worker effect (SMR=82, 95% CI = 72-91).[98]

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.[91] 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.[99] 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).[90] 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.[100] However, mortality for heart disease among firefighters peaks from noon until midnight and corresponds closely to the frequency of emergency calls.[91] Likewise, seasonality of deaths from heart disease among firefighters also shows an anomaly, demonstrating two peaks, in January-March and in July-August [101], 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.[2, 19] 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.[102] 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.[103] 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 are 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.[104] (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.

Table 4. Cardiovascular Deaths in Service and Firefighting Duties at time of Death, after work by Kales et al.[90]

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.

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.

TOXIC EXPOSURES: ACUTE EVENTS

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.[106] 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.

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. 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.

Fine and Ultrafine Particulate Matter

Combustion 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.) Fine particulate air pollution has ben extensively studies because it is known to be associated with mortality and illness in the community. Particulate matter in the same size range and with similar composition is generated by combustion in fires. 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.

TOXIC EXPOSURES: UNDERLYING DISEASE

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.

Carbon Monoxide (Not confirmed)

In the 1970's carbon monoxide was thought to promote atherosclerosis, as a result of the unconfirmed work of one investigator (Aranow: references to his work have been withdrawn). Deficiencies in data collection and reporting were identified in his work, which at the time played an important role in setting standards for environmental air pollution. Others could not replicate his findings and so these findings are no longer cited or deemed credible.

Polycyclic Aromatic Hydrocarbons (PAH)

Among the many toxic exposures to which firefighters may be exposed, polycyclic aromatic hydrocarbons (PAHs) have 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. Brominated compounds have been used in the past as fire retardants. Although some of the polybrominated biphenyl compounds may be quite toxic, exposure to brominated compounds does not seem to be appreciable risk associated with firefighting.

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°. Below this temperature window, they do not form efficiently and above the window they break up and so do not persist. Many of the congeners (210 each) are toxicologically irrelevant. A few are highly toxic and the cardiovascular system is one important target organ. Presumably due to induction of liver cholesterol-forming activity and local effects on the blood vessels favoring atherosclerosis, dioxins 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.[107] 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.

Polychlorinated biphenyl compounds (PCBs, of which there are 209 congeners) are not formed in settings of combustion but maybe released, particularly in fires involving electrical transmission and old transformers. Some of the PCB congeners act much like the dioxin congeners described above.

PHYSICAL FACTORS

Fire suppression, training, and rescue, in particular, place extreme demands on firefighters, close to the limits of endurance. The principal concern is that the following physical factors occur simultaneously and may individually and in combination confer a risk of heat-related outcomes (exhaustion and possibly potentially lethal heat stroke), degrade performance dangerously, impose increased myocardial oxygen demand, induce arrhythmias, and increase the risk of injury:

- Metabolic demand
- Dehydration
- Muscle exhaustion
- Hyperthermia due to inability to achieve efficient heat loss
- Ergonomic demands for working in tight or difficult places

During active fire suppression, firefighters are simultaneously exposed to radiant and convective heat, insulated against evaporative heat loss by their turnout gear, burdened with increased weight and exertion (especially during rescue), and dehydrated through perspiration, often markedly so. These factors impose a substantial load on the heart by, respectively, inducing reactive vasodilation and therefore a fall in blood pressure with compensatory tachycardia, maintaining body heat and preventing heat loss so that vasodilation and cardiac stress are present simultaneously, increasing myocardial oxygen demand, and reducing cardiac output by depleting volume. The result is cardiac stress close to the maximum that is physiologically sustainable for a short period and that demonstrably degrades performance.[94, 108-110]

Specific duties of firefighting are closely associated with mortality from cardiovascular events on duty.[90, 111] These are summarized in Table 1. It is apparent that fire suppression which constitutes a small fraction of the activity time of a firefighter but is intense and requires exertion, is highly disproportionate in association with on-duty deaths from cardiovascular causes, well beyond the range that would suggest confounding or bias and convincingly causal, almost certainly as a triggering factor or proximate cause in the presence of existing coronary artery disease in the majority of cases. In a minority of cases, the effect of fire suppression may plausibly be the result of heat stroke, carbon monoxide toxicity, or possibly cyanide toxicity (depending on fire characteristics). It is therefore incontrovertible that physical factors associated with firefighting are associated with acute and fatal events.

Current guidelines of the National Fire Protection Association require 20 minutes on SCBA to be followed by 10 minutes of recovery before resuming exertion with another 20 minutes on SCBA. However, simulations with optimal hydration have demonstrated that this may not be enough recovery time.[69] Because performance declines quickly, the heat-related exhaustion of capacity associated with maximum exertion in firefighting is a serious safety concern, since it affects how well firefighters can protect themselves, manage escape or rescue, and still fight the fire.

Firefighters lose copious amounts of fluid during intense exertion in heat during fire suppression. It has been established that the form and route by which the depleted volume is restored makes no difference in restoring performance.[69]

METABOLIC RISK FACTORS

Firefighting is an occupation that requires high levels of fitness for safety and performance. However, fire departments have only recently adopted stringent requirements for fitness to work and often do not apply them as rigorously to veteran firefighters, who are in any case likely to be older, than new hires. As a consequence, current data reflect a mixed population and may underestimate risk for older firefighters while overestimating risk for younger firefighters.

Fire departments and firefighters' unions recognize the importance of cardiovascular fitness as well as strength and endurance and are well aware of controversies with respect to cardiovascular disease. Contemporary firefighters are encouraged to, and do, work out in exercise rooms while on duty, during periods between alarms. The proportionate mortality from "heart attacks" is higher in all age groups for volunteer firefighters (50%) compared to career firefighters (39%), suggesting a strong fitness effect.[112]

However, the transition to increasing fitness requirements is still underway, and as of 2007, more than 70% of fire departments were reported to have lacked mandatory fitness standards and

requirements for physical exercise. Periodic health surveillance or fitness evaluations, alone, have been found to be ineffective in identifying firefighters at high risk of early retirement or disability due to ill health.[113, 114] Even so, studies of the prevalence of cardiovascular risk factors have come from the minority that monitor their firefighters and do have such requirements. It is therefore puzzling that the distribution of risk factors among firefighters is not better than reported. One reason may be that available studies, which are primarily prevalence and group mean data, data, are obscuring cohort trends. A competing hypothesis is that firefighters are more influenced in matters of nutrition by community attitudes rather than by health promotion initiatives. The data are unclear on which is the more likely explanation.

Firefighters, as a population, are almost exclusively male (there are exceptions and this is changing), most active between the ages of 30 and 55, and highly fit when they enter fire service. In recent years, fire departments have individually strongly encouraged participation in fitness programs and have introduced mandatory health and fitness evaluations, for the specific purpose of ensuring fitness for duty over the firefighter's career. The content and rigor of these programs have varied but over time they are becoming more standardized. They are applied most consistently to younger firefighters because they can be imposed as a legitimate work requirement at the time of hire, reflecting documented criteria for fitness for duty, but it is difficult to impose such a requirement retroactively for veteran firefighters who have already demonstrated their ability to do the job. Historically, the fire service has usually dealt with lack of fitness informally, by reassigning personnel to less demanding jobs. As a consequence, the current population of active firefighters outside of administrative positions is a relatively young but still mixed population, increasingly retained on evidence of fitness during the course of their career as well as selected for this at the time of hire.

Firefighting is associated with lifestyle issues arising from the characteristic pattern of long periods of sedentary waiting punctuated by highly stressful mobilization for an alarm. Particularly in the past, when health consciousness was not as developed, this lifestyle may have promoted overeating or maladaptive nutritional choices[115] and the risk of obesity and provoked transient hypertension, these consequences possibly contributing to the risk of chronic hypertension.[116]

Extensive profiling of firefighters in prevalence studies have suggested that firefighters are an anomaly, in that their occupation requires high levels of fitness but their distribution of risk factors is adverse, with cardiovascular risk factors in excess of the general population and much higher than Healthy People 2010 targets.[117, 118] In one comprehensive but relatively small study from Chicago, the least favorable cardiovascular risk was seen in firefighters aged 45 to 49, with 79% exceeding a "low" projected risk, much of which was apparently driven by elevated triglyceride levels and LDL cholesterol (which, unfortunately, were not reported).[118] This is unexpected. As firefighters became more committed to fitness in this generation, metabolic indicators therefore should have become more favorable over time but the factors contributing to the potential contribution of transient stress-related hypertension should not have changed.

In fact, the trends that have occurred do present a mixed picture in the last decade. Blood cholesterol levels over time seemed to be declining in a Massachusetts[119] but not in a Scottish cohort[113, 114]. Not surprisingly, obesity rates in both were rising and more firefighters were showing elevated triglycerides. Firefighters in western Scotland, where elevations in cardiovascular risk factors are particularly prevalent, also showed no group improvement in cholesterol from age 40 to retirement despite a health education program.[113, 114] This suggests that firefighters remained more heavily influenced by community risk trends for cardiovascular risk factors in that era than by programs that raise awareness and promote healthful behavior and fitness.

The most plausible explanation for the unclear picture and the absence of demonstrable improvement despite the obvious interest and commitment to fitness for duty among contemporary fire departments and firefighters is that it is an artefact of the data. One wonders if there is a cohort effect underlying the prevalence. The recruitment effect is certainly stronger than the retention effect in favoring fitness. Younger firefighters have been subject to an intense selection effect at the time of hire for many years. Older firefighters, on the other hand, may have been subject to only a relatively mild retention effect as they aged (with only those with overt, symptomatic disease migrating out of the fire service). However, firefighters who entered the service twenty years ago may now represent a cohort that was fit when it began but entered the entered the fire service when standards for maintaining fitness were not high or enforced. This hypothetical cohort would still be below the age at which their absolute risk for heart disease would be causing sufficient morbidity and disability that a retention effect could be observed. This hypothesis could be tested if firefighters who entered fire service from, say, 1960 were tracked as cohorts.

A minority of firefighters, which appears to be increasing, shows patterns of high risk for cardiovascular disease.[119, 120] In one study of 214 firefighters in Colorado, 15% were found to meet the working definition of "metabolic syndrome", compared to 24% in the general population. The firefighters without the metabolic syndrome predictably showed significantly more favorable levels of weight, BMI, body composition, waist circumference, triglyceride level, exercise tolerance, and both systolic and diastolic blood pressure. Blood cholesterol and fasting glucose levels were also lower but the differences did not achieve statistical significance. The healthy firefighters without metabolic syndrome drank less alcohol and smoked less, as a group.[121]

Blood pressure is a particularly critical risk factor for firefighters because of its demonstrated association with adverse outcomes, not only related to health, suck as increased frequency and duration of sickness absence, but also to termination of employment. One explanation is that firefighters with untreated hypertension are more likely to have inadequate treatment of other health problems.[122]

Hypertension appears to be particularly prevalent among emergency response personnel, including firefighters, where the development of chronic hypertension appears to follow low-grade elevations in blood pressure at or just below the usual cut-off points for treatment ("pre-hypertension"). The majority of events occur in this group, not among firefighters with clinical hypertension.[116] It has long been postulated that this subclinical or borderline hypertensive tendency may reflect the cumulative effect of episodic, unpredictable bursts of activity and exertion. Borderline and even clinical hypertension are widely unrecognized in firefighters, with about 20% prevalence of hypertension, mostly undiagnosed, and undertreated, with as many as 80% of hypertensive firefighters being untreated or inadequately treated in one population.[123]

Oddly, there are rather few studies that report on cigarette smoking prevalence of consumption among firefighters. The few that do[124] do not suggest that tobacco consumption is any higher than in the community and may historically have been lower than in the general population.

Studies that have compared industrial (private sector) and municipal firefighters suggest that exercise is more consistent and intense when firefighters are encouraged to work out while on duty, a prospect that is entirely feasible because of the work organization characteristic of firefighting.[125]

OTHER OBSERVATIONS

In the course of preparing this report, other observations were made that may be useful.

Work-Relatedness

35 US states currently have statutory presumptions of work-relationship for firefighters who develop cardiovascular disease, 11 specifically for hypertension, and 11 states have similar presumptions for police.[11 116, 126]

For purposes of recording and compensation, since 2003 the US Fire Administration considers a death from "heart attack" to have been on-duty if it occurs within 24 hours of an alarm. Prior to 2003, there was an additional requirement that symptoms begin during the event.[127]

The 24-hour criterion is arbitrary, and presumably was developed largely for administrative purposes. To the extent that inflammatory processes are at work (due to ultrafine particulate matter, coagulation and inflammatory components of coronary thrombosis, and induced by smoke inhalation), a 24-hour would be quite short to accommodate the window of vulnerability to acute cardiac events following response to an alarm or an event of smoke inhalation. The usual time course for short-term inflammatory events is on the order of days and is highly variable. For work-relatedness for purposes of compensation, therefore a 72-hour window would be more realistic.

Gaps

Future studies of cardiovascular risk factors among firefighters should go beyond prevalence whenever possible and try to reconstruct cohort trends, in order to clarify the current, undoubtedly mixed picture of the distribution of risk in this occupation. Whenever possible, data should be adjusted by age, for fire department policies on fitness, and for volunteer or career status of firefighters.

Facilities and policies encouraging firefighters to work out with exercise while on duty are associated with greater compliance with exercise routines and are likely to lead to better outcomes and lower risks. They are therefore to be encouraged among fire departments as an investment in public services.

Hypertension is widely unrecognized and undertreated among firefighters. A concerted program of aggressive control of blood pressure among emergency responders is a priority for management of this population.116

CANCER RISK

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.[128] 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[57] 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.[129]

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) and polycyclic chlorinated biphenyl compounds (PCBs) and their corresponding furans
- Carcinogenic chemicals arising from work as a firefighter, including diesel exhaust.

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.[71]

The PAHs are a large family of organic compounds, several of which are known carcinogens:

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

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.

Benzene is a cyclic (but not polycyclic, meaning that it only has one ring) aromatic (meaning that it has a shared electron structure in the ring) hydrocarbon. 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.

Asbestos would be most commonly encountered incidental to fighting fires in older buildings with structural insulation using asbestos products. Asbestos does not need definition for professionals in Quebec. 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 nonmalignant lung disorders. While contemporary firefighters are unlikely to be heavily or repeatedly exposed to asbestos, they would be exposed on occasion to this known carcinogen.

Formaldehyde may or may not be a significant risk. Although formaldehyde is a known nasal carcinogen in rodents and a suspected 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 is most likely in lung cancer risk.

Recently, a paper appeared by the former director cancer surveillance and the registry of Washington state[42] 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. 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 firefighting. 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

In this paper, the risk estimates will be presented as they were reported in the original paper. SMRs are given to three places, without decimals, or expressed as relative risks as in Baris et al.[18] Relative risks are given as decimals, with no qualification. Odds ratios are given as decimals and identified as such.

Table 1, earlier in 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.[88] 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 reference32 has been rediscovered. They are summarized below.

Giles et al.[32] 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 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 and there was no follow up in the world literature.

Burnett et al.[59] 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.[130]

Deschamp et al.[97] 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.[131] 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.[131] found an excess of cancer of the brain, specifically, in African-American but not white firefighters. This is an interesting and provocative finding. The proportion of black Canadian firefighters in the Canadian fire service is smaller than the proportion of African Americans in the United States because of demographics of the population as a whole, so the implications of racial disparity for the overall risk associated with firefighting as an occupation are unclear.

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. 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, 95% 0.7 – 1.8), which showed a modest increase with duration of service, bladder (1.14, 95% CI 0.4 – 2.7), brain (1.27, 95% CI 0.4 – 3.0), and "myeloleukemia" (1.81, 95% 0.5 – 4.6), but not kidney (0.57, 95% CI 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, 95% CI 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, 95% CI 0.3 – 9.8) but less than expected for lung (0.86, 95% CI 0.4 – 1.6), brain (0.68, 95% CI 0.1 – 2.4) and "hematopoietic cancer" (0.72, 95% CI 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)[18] 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.[18] 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 (SMR=1.51; 95% CI =1.18-1.93). Nonsignificant excesses were reported for cancers of the buccal cavity and pharynx (1.36; 95% CI=0.97, 2.14); for non-Hodgkin's lymphoma (1.41; 95% CI=0.91, 2.19); for multiple myeloma (1.68; 95% CI=0.90-3.11) and for lung cancer (1.13; 95% CI 0.97-1.32). With >20 years of firefighting, the following cancer sites showed elevated risks: colon cancer (1.68; 95% CI 1.17-240); kidney cancer (2.20;

95% CI 1.18-4.08); non-Hodgkin's lymphoma (1.72; 95% CI 0.90-3.31); multiple myeloma (2.31; 95% CI 1.04-5.16); and benign neoplasms (2.54; 95% CI 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 nonexposed. 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 (nonexposed) 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[18], 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[60] 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, 95% CI = 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; 95% CI = 1.01 – 1.62) and testicular tissue (1.60; 95% CI = 1.20 – 2.09), and yielded an unanticipated finding, thyroid (3.97; 95% CI = 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[133], 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.[134] 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.[135] 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.)

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.[96], while a fine and competently-executed study, is consistently lower in its risk estimates for disease outcomes compared to other studies of firefighters. This is also evident in the comparison of 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[136] or a disease registry[137]. 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[138], 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[138] examine both usual and current occupation and registry studies are known to be subject to deficiencies in case ascertainment[134].

Another example of how individual studies on firefighters may be similar but not necessarily alike in important respects is a study by Eliopulos et al.[139]. This study is commonly included in reviews of the risk of firefighters but its subjects were brush-fire fighters, who work in the open air and are exposed to burning vegetation which, like wood, tends to have a lower carcinogenic risk than many synthetic materials. The profile of combustion-related exposures is rather different than urban firefighters.[3, 140]

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. 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 reasonably easy to interpret by tumor site.

Bladder cancer

Burnett et al.[59] 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.[60, 131] 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.

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 our data from Alberta[141] bladder cancer did not appear before age 60 or before 20 years of service and showed a very long peak latency of 40 years.

Improving the exposure assessment and examining subgroups experiencing higher exposure increases the risk estimate in Baris et al.[18] reported a slightly elevated SMR of 1.25 for bladder cancer, with greatest risk being among those hired before 1935 (SMR=1.71, 95% CI=0.94, 3.08), and among those with greater number of runs during their first 5 years employed (SMR=2.59, 95% CI=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.[142] 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.[60, 131] demonstrated a significantly increased risk for bladder cancer among both male and female firefighters in Florida (male: SIR = 1.29, 95% CI=1.01, 1.62; female: 10.00, 0.13 – 55.60, based on a single case). Kang[134], with much smaller numbers, demonstrated a similar but not significantly elevated risk when firefighters were compared to police (SMOR=1.22, 95%CI:0.89-1.69) and to a referent population (SMOR=0.93, 95% CI = 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.[135] 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, 95%CI = 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 may be of interest that one Canadian study[142] of incident cancer shows an elevation in risk for firefighters (SIR=1.51, 95% CI = 0.59-3.84)).

The products of combustion most relevant to bladder cancer are polycyclic aromatic hydrocarbons, which are produced in abundance from burning structural materials, particularly at middle-range fire temperatures and are constitutents of diesel exhaust.

McGregor (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.[15] 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.

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.

Kidney cancer

Cancer of the kidney has become widely accepted as associated with firefighting by conventional criteria.[57]

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 carcinomas, which arise from the renal pelvis (the funnel-like collecting system) and are similar to cancers of the ureter and bladder (collectively called urothelial cancers). Other forms of cancer arising in the kidney are rare. 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 transitional 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. In fact, there is an increased risk of urothelial cancers – see bladder, above – but it is in the direction of increased risk anyway and so a presumption would still hold if the risk is similar to bladder (as it probably would be). 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 summary, the inclusion of transitional cell cancers of the renal pelvis in the ICD code for kidney cancer is not a serious objection to a presumption of risk.

Burnett et al.[59] 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.[60, 131] 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[143] examining occupational associations of renal cell cancer cases demonstrated a highly elevated and highly significant relative risk for firefighters (OR=4.89, 95% CI = 2.47-8.93).

The standard cancer epidemiology text Schottenfeld and Fraumeni[144] cites several studies in which a near doubling of risk is associated with duration of employment less than ten years, among the aluminum workers exposed to polycyclic aromatic hydrocarbons. These are likely to be the responsible carcinogens in firefighting. In data from Alberta[141] a marked elevation in risk for kidney cancer was visible in the category 10 – 19 years of employment. Baris and co-workers[18] reported a doubling of risk with an SMR=2.20, 95% CI=1.18, 4.08 among those employed for 20 or more years.

Ma et al.[60, 124] 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, 95% CI=0.05, 23.18). Kang[134], 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, 95%CI:0.90-2.01) but not to a referent population (SMOR=1.01, 95% CI = 0.74-1.38).

Ahn et al.[135] demonstrated an overall elevated risk for kidney cancers 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 kidney cancer (SIR = 1.59, 95% CI = 1.00, 2.41).

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.

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[145], 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 [146] 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[147] 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.

Many of the findings in Pesch et al.[148] study regarding occupational exposures and renal cell cancer are contradicted by an earlier Danish study[149] but neither specifically studied firefighters. The two investigators came to opposite conclusions with respect to the role of both hydrocarbons and asbestos in their own populations, but both admitted that their particular study was not definitive. Mellemgaard et al.[149] also found an association (not statistically significant, however) with exposure to hydrocarbons, although they did not study firefighting among their occupations with an a priori expectation of elevated risk. This is because the recognition of an elevated risk among firefighters had only been made the year before, so they did not flag it for attention. That same year, McLaughlin [150, 151] concluded that "Risk of renal-cell carcinoma was found to be associated with employment as a truck driver, exposure to gasoline, *other hydrocarbons...*" [italics added], a significant observation considering the exposure profile for firefighters. Both papers predate recognition of the association for firefighters.) A recent study of workers in Eastern Europe exposed to polycyclic aromatic hydrocarbons [152] did not show an elevation in kidney cancer but the exposure assessments were limited to employment characteristics and could not be validated.

However, 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.

Testicular Cancer

The International Agency for Research on Cancer (IARC) already recognizes an association between testicular cancer and occupation as a firefighter.[129]

Bates et al.[132] found an odds ratio of 3.0 (95% CI = 1.3 – 5.90) for testicular cancer among firefighters in the New Zealand capital city of Wellington. Stang et al.[153] reported very similar findings from northern Germany, although their odds ratio of 4.3 (95% CI = 0.7 – 30.5) was not statistically significant. 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.[153, 154] 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 [133, 154] then demonstrated a statistically significant elevation for testicular cancer among California firefighters (OR=1.54, 95% CI = 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.

Biological credibility for the association, however, comes from the observation by Olshan et al. [155] that the offspring of male firefighters (the great majority are male) are at significant and substantial elevated risk for birth defects, specifically common cardiac anomalies (for atrial septal defects, an odds ratio of almost 6). Such a finding, implying a congenital birth defect mediated by a male factor, points to an effect at the testes or, less plausibly, in seminal fluid.

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.

Testicular cancer represents a good example of the “first case” problem. When the first case of a previously unrecognized association is asserted in a legal action or a claim is filed, the literature is undeveloped and therefore does not support it. The first case is almost always denied. If the case is decided in litigation, this closes off access to any future remedy because the case has already been decided. Unless there is a provision in a workers’ compensation system that requires the system to reopen claims, the rejected claimant goes without compensation regardless of the subsequent accumulation of evidence. A publicized first case often stimulates further research but this usually comes too late for the initial claim.

Although the presence of exposures known to cause testicular cancer cannot be documented for firefighters, there is strong evidence of an elevation in the literature that exceeds the criterion for a presumption. The preponderance of evidence favors causation and sufficient weight to derive a presumption.

A paper that has on occasion been used to rebut claims for this 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., like Lipworth [145, 157], are 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.

Prostate Cancer

The question of prostate cancer has come up repeatedly and has been exceptionally difficult. On the face of it, the evidence would seem to suggest a rather weak association with toxicological plausibility. However, cancer of the prostate presents special problems that call even this conclusion into question. 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. Prostate cancer does not fit the framework outlined in this report. Thus, prostate cancer requires exceptionally extensive discussion and documentation.

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.

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 would be much higher and more accurate reflect the true prevalence.

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 would not be expected to pick up a screening effect because wellness and screening programs for firefighters were not common at that time. In general, with the exception of Giles et al. (1993)[32] and Demers et al.(1994)[158], studies conducted of firefighters before 1990 show no apparent increase in frequency of prostate cancer. (On the other hand, the elevation seen in Grimes is quite high, and occurred in Australia, which had a national health service by 1980, making this study the most significant anomaly.) 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.

The International Agency for Research on Cancer IARC (IARC Monograph No. 98, 2007)[159] recognizes two studies that show an association between prostate cancer and occupation as a firefighter, Krstev (2008)[160] 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. 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. (1994)[158] found that the observed elevation (relative risk 1.4) in prostate cancer demonstrated in his population of Washington state-based urban firefighters was much reduced when compared to police officers, rather than the general population. 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)[160] 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. 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. (1998)[38] found elevations in prostate cancer in both white and African-American firefighters but the elevation was small (mortality odds ratio 1.2). The frequency of prostate cancer is elevated in African Americans in the general population, as is mortality from the disease, a situation which persists.[161] 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 [162], firefighters had a lower rate than the reference population. However, the study was obviously underpowered and because of its unusual design features, bias was difficult to interpret. Zeegers conducted a prospective (cohort) study of prostate cancer risk, using incidence, also in the Netherlands, of men aged 55 to 69 in 1986.[163] They 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%, but this was not obviously a source of bias because they found moderate reductions in risk among firefighters in their cohort. This study was therefore even more under-powered than usual for the detection of infrequent outcomes in individual occupations. Rubber workers (the definition of which was "ever worked in the industry, rather than usual occupation), in this cohort demonstrated a very high RR=4.18 and yet it did not achieve statistical significance. (Rubber workers have been known in the past to have elevated rates of prostate cancer in many studies in other countries.) This suggests that although the study was large, the power to detect an excess in any one occupation was low. 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.[164] What this all means for firefighters is not entirely clear but should be considered weak or negative evidence for an association with prostate cancer.

Bates et al. (2007) demonstrated a statistically significant elevation for prostate cancer among California firefighters (OR=1.22, 95% CI = 1.12-1.33).[25, 163]

A persuasive study that illustrates the complexity of the issue is that by Ahn et al. (2012)[135] on Korean fire-rescue personnel, who 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.

Other studies have not reported an association.

Conducting a meta-analysis of the literature up to that time, LeMasters et al. (2006)[56] found an elevation of a magnitude slightly under 30% (relative risk 1.28) for prostate cancer among firefighters. In my opinion, that finding may be true, given statistical uncertainty (overall the LeMasters study is well done but places too much confidence in the methodology of meta-analysis) but its findings do not necessarily mean that prostate cancer is associated with exposures that arise out of firefighting. It probably means that the detection of prostate cancer is much more efficient in firefighters and other municipal employees who are ensured

and participate in screening programs than in the general population, in which there are many uninsured and screening for prostate cancer is highly variable and often skipped.

Population-based occupational cancer studies are usually unsatisfactory because of low power to identify associations for any given occupation. One possible exception was 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."[165] The absence of an occupational association would include firefighting.

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.

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 what are called "indolent" or latent", meaning that they grow slowly and are not aggressive.

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.[166,167] 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.

In Canada, where residents enjoy equitable access to healthcare and there is less difference 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.[171]

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 is conducted.[172] No surprisingly, more cases are observed in such populations.

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.

The criteria for a presumption for purposes of general causation rests on the demonstration that occupational risk factors in the majority of cases that arise from that occupation contribute a greater risk than the background risk factors that operate in the general population. For prostate cancer and firefighting, this cannot be demonstrated.

If firefighting were associated with prostate cancer to a degree that would warrant a presumption and that would imply that firefighting is the main cause of the disease among firefighters, one would expect a risk estimate close to a doubling (a relative risk of 2), with allowance for statistical uncertainty and bias. Only Giles suggests this level of risk without the complicating factors of screening effects.[32] the relative risk in the LeMasters study was 1.28, for an attributable risk of 22%, which falls well short of the magnitude one would logically require for a presumption.[56] None of the individual studies they entered into the meta-analysis showed a risk even approaching that magnitude, either. Therefore, the evidence for an association with firefighting would not be strong enough to satisfy the criteria for a presumption, even if one assumed that firefighters were not subject to more intensive screening.

Taken together, the literature on prostate cancer could be construed as suggesting an association but falls well below a balance of probabilities. 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 very high. However, a presumption based on general causation is not obviously justified.

There are several lines of argument that might support specific causation in an individual case that has characteristics suggesting an occupational association (such as exceptionally young age at detection or intensity of exposure).

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. This raises the possibility that 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.

For the most part, prostate cancer is not closely or consistently associated with any known carcinogen, 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.[173] 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.[174]

Studies of one occupation with intense exposure to PAHs as high as for firefighters did suggest an increased risk for mortality from prostate cancer but there was no elevation in incidence of the cancer. Sims et al. found a strong association between risk of death from prostate cancer and production work in "prebake" aluminum smelting[175], which is not characterized by intense and chronic exposure to PAHs that was seen in the industry in a previous technology, the Søderburg process. If a significant number of these workers were older and had prior experience working in Søderburg plants, however, it could account for an elevation in mortality but not incidence. The study was conducted in Australia, where features of the health care system are likely to reduce the screening bias. Other studies of prebake aluminum smelting workers do not show an elevation.

An important line of evidence on cancer risk for firefighters involves prostate cells but should be understood to be of questionable and possibly marginal relevance to prostate cancer as such. The study was performed on cultured cells from the prostate gland, examining mechanisms for altering gene expression ("epigenetics") rather than altering the gene itself.[176] Ouyang et al. (2012) found that firefighters had a higher prevalence of expression of a particular gene (phosphatase 22 promoter) that has been associated with increased cancer risk. This finding was associated with "hypomethylation" (a reduced methyl "tag" attached to bases in DNA in the sequence coding for the expression of the gene). The degree of hypomethylation correlated with the duration of service as a firefighter but not with the age of the subject. The effect could be reproduced by exposing the cells to benzo[a]pyrene, a known carcinogen commonly found and always present among the polycyclic aromatic hydrocarbons from combustion sources. The conclusion of the authors was that cumulative exposure to PAHs during firefighting can cause epigenetic changes in promoters of specific genes. This is an interesting and provocative study but far removed from the living human prostate cell, which is surrounded by other tissue and is responsive to many influences, including hormones, but generally shows little responsiveness to human carcinogens in population studies. The true significance of this study is that it shows that cells deep in the body, not just in the lung or skin, are affected by exposures consistent with firefighting in a way that predisposes to cancer risk. It is not necessarily a smoking gun for prostate cancer. The exposure level in the experimental cannot be easily related to occupational exposures and the article does not compare dose delivered at the level of the cell.

The conclusion to be drawn from these studies is that it is possible 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 presumption or conclusion of general causation.

BRAIN

Youakim[57] and LeMasters et al.[56] both demonstrated elevations in risk for brain cancer among firefighters using conventional criteria of meta-analysis.

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 brain tumour types. 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 meningioma) that are not associated with environmental or occupational factors.[177] 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 not be done anytime soon if ever.

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.[16] 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 action of a putative carcinogen.

A different approach is required to determine occupational risk within this category of tumorurs, 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.

Bates (2007) [133] demonstrated a statistically significant elevation for brain cancer among California firefighters (OR=1.35, 95% CI = 1.06-1.72). Krishnan (2003)[178] 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, 95% CI = 0.70-4301) and ever-employed (OR=2.85, 95% CI = 0.77-10.58), but the study design was intrinsically low-powered for any one occupation and neither achieved statistical significance. Kang[134] found a statistically significant elevation in risk among firefighters in Massachusetts compared to police (SMOR=1.90, 95%CI:1.10-3.26), which remained elevated but lost significance when compared to a referent population (SMOR=1.36, 95% CI = 0.87-2.12). Thus there appears to be considerable consistency in the risk estimates for this aggregated cancer category within positive studies.

Ma et al.[131] reported that no elevation was observed for brain cancer among white firefighters. In her study of Florida firefighters[60, 124] she found a deficit (SIR=0.58) among men and no cases among women firefighters. Burnett[59] did not observe an elevation for cancer of the brain.

Baris et al.[18] observed a relative deficit of brain cancer, with an SMR of 0.61 (95% CI 0.31-1.22). 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 contradict 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 weight of evidence to date, predominantly from earlier studies, suggests that the elevation in risk for brain cancer reflects a true risk which may be concentrated in certain subgroups, as demonstrated among black firefighters.

Notwithstanding that current information does not identify a single putative causal agent, given the presence of exposures known or suspected to cause cancer of the brain and to act on the astrocyte, and given evidence of an elevation in the literature that suggests dilution of a true risk that approaches the criterion for a presumption, the preponderance of evidence favors causation and sufficient weight to derive a presumption.

Demers et al.[179] documented a doubling or risk (SMR 257) at less than ten years of employment peaking at over a tripling (353) up to 19 years. Heyer et al.[180] also showed a near-doubling of risk (184) at less than 15 years duration of exposure. 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. Youakim, in his meta-analysis, showed that firefighters with over 30 years of service were most at risk.[57]

LEUKEMIA, LYMPHOMA, MYELOMA: AN ILLOGICAL COMBINATION

This disease aggregation represents the most difficult interpretive situation because of the medical heterogeneity of the rubric and remains refractory to efforts to tease out which individual diseases that are driving the elevated risk.

“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 (2007) already recognizes an association between non-Hodgkin’s lymphoma and occupation as a firefighter.[129] Both Youakim[57] and LeMasters et al.[56] recognized a significantly elevated risk by conventional scientific criteria in their meta-analyses. McGregor, on the other hand, concluded that the evidence was insufficient to come to any recommendation.[14]

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.

Epidemiological studies generally do not separate the various types, or if they do, 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 this literature is not ready for evaluation, in our opinion.) 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.[23] Non-Hodgkin's lymphoma is further divided, especially in older epidemiological studies, into the obsolete categories "lymphosarcomas" and "reticulum cell sarcomas", which are only slightly more informative than the aggregated rubric. These classifications are no longer accepted clinically and were always understood to be approximate, aggregating together various specific lymphomatous diseases.

This crude system obscures the level of risk that may exist for certain critical types of lymphoma. 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 with solvent exposure.[23] 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 is clear, therefore, that combining all lymphomas will not yield an meaningful measure of risk for etiological research, regardless of the statistical advantages of aggregate numbers.

The broad group of large B-cell lymphomas is itself thought to be a heterogeneous group of cancers, not a single disease. (Guraxani, 2009) Clearly this is a very heterogeneous category.

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 every lymphoma 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 common 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.

Current thinking on the etiology of lymphomas suggests that alterations in immune stimulation, suppression or modulation are the key events in the disease.[181] 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.[59], which revealed an elevation for non-Hodgkin's lymphoma. 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.[131] 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.[60, 124] found no elevation among men (SIR=1.09, 95% CI = 0.61-1.80) but a large elevation among women firefighters (SIR=33.30, 95% CI = 0.44-185.00) based on a single case. (Ma also found an elevation in risk for Hodgkin's disease, SIR=6.25, 95% CI = 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.[18] 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 (95% CI 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 (95% CI 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, 95% CI=0.90,3.31). This suggests the possibility that these are true elevations in these subgroups.

Among population monitoring studies, Figgs et al.[182] found an extraordinarily high and highly significant risk of non-Hodgkin's lymphoma in firefighters in 24 states (MOR=5.6, 95% CI = 2.5-12.3).

Ahn et al.[135] 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, 95% CI = 1.12, 2.76).

Not much is known of the 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 may be associated with elevation in risk of non-Hodgkin's lymphomas in other settings.[183] Almost nothing is known of elevations in specific lymphomas, so all evaluation is essentially based on the grouping as a whole. Indirect evidence exists for large B-cell lymphomas explains why a true elevation in this most common lymphoma could be as high or higher than the criterion for a presumption and still be overlooked. Giving the benefit of the doubt to the worker, the preponderance of evidence favors causation and sufficient weight to derive a presumption.

Another way to look at the problem of non-Hodgkin's lymphoma among firefighters is as follows: that it cannot be rebutted on the basis of general causation that a non-Hodgkin's lymphoma arose from his occupation as a firefighter. Furthermore, not only proof of causation, which is a higher standard, but also demonstration of causation to a balance of probabilities is technically impossible at this time and so beyond the capability of any claimant, because direct evidence is lacking. The weight of what indirect evidence exists therefore suggests that cancers in this category can arise from occupation as a firefighter.

The latency period for non-Hodgkin's lymphoma appears to be very long in most cases. The minimum latency is unclear.

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 is known to be associated with benzene exposure. 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.[17] 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.[56]

Haematopoietic cancers were separately addressed in Burnett et al.[59], who 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. With 33 and 61 deaths, respectively, this is a large collection of deaths by leukemia. Ma et al.[131] observed no apparent elevation for haematopoietic cancers, with an MOR of 1.1 among white firefighters. Among Florida firefighters[60, 124], she observed no elevation in male and no cases in female firefighters.

Baris et al.[18] found no overall elevation for the leukemias (SMR 83, 95% CI 0.50-1.37), not specified as acute or chronic or by type. A statistically significant elevation in SMR of 275 (95% CI 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 (95% CI 0.70-8.54) and with medium

(but not high) levels of runs over a lifetime, with SMR of 2.50 (95% CI 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.[18] does not really clarify this issue.

There is also an important anomaly in the older literature. L'Abbé (whose married name was Aronson) and Tomlinson[184], in a study of firefighters in Toronto, uniquely reported risk for types of leukemia. They observed an excess of "lymphatic" [lymphocytic] leukemia at 190 (42 – 485). This finding was highly influential in the IDSP report, 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 L'Abbé and Tomlinson[184] 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 for historical reasons and because of their clinical manifestations. McGregor concluded that there was no evidence supportive of an association, based on the standard of scientific certainty.[17] However, Baris et al.[18] found an overall excess (SMR=1.7, 95% CI = 0.9-3.1) increasing with duration of employment, with 20+ years having a borderline statistically significant SMR of 2.31 (95%CI = 1.0 – 5.2), and a statistically significant SMR of 2.54 (95% CI = 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). This pattern is suggestive of a strong association that cannot be dismissed as confounding.

The weight of direct evidence suggests that cancers in this category can arise from occupation as a firefighter. 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.

Another way to look at the problem of myeloma is that it also resembles non-Hodgkin's lymphoma among firefighters in that it cannot be rebutted on the basis of general causation

that a myeloma arose from his occupation as a firefighter.

The latency period for non-Hodgkin's lymphoma appears to be very long in most cases. 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. Thus, the earlier recommendations for a presumption[177, 185] for an implied presumption but with individual evaluation of each case, are not contradicted by the new evidence. Because the individual disease risks cannot be separated, they must be taken as a group until more information becomes available. The National Cancer Institute (US) has been pursuing research in this area (especially the lymphomas, and associations with agriculture) vigorously in recent years and may provide further insights in the future. It is possible but unlikely (after consultations with the group) that the large multicentre NIOSH study will examine individual diseases within these groups to attain finer resolution.

LUNG CANCER

Lung cancer presents a different problem. In this case, the risk associated with occupation is overwhelmed by the effect of cigarette smoking. A different approach must be used.

Lung cancer has been the most difficult cancer site to evaluate in epidemiologic studies of firefighters. Despite the obvious exposure to carcinogens inhaled in smoke[3, 186], it has been difficult to document an excess in mortality from lung cancer of a magnitude and consistency compatible with occupational exposure. Studies we conducted in Alberta on fire fighters entering the fire service from 1927 to 1987 do show evidence for an increase in risk.[141] 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 [18] , do not observe elevations. On the other hand, Ma et al.[60, 124] describes no elevation in risk for male firefighters in Florida and the usual moderately elevated risk (SIR=1.40, 95% CI = 0.28-4.08) for females, who in general entered the fire service more recently.

Without question, cigarette smoking complicates the analysis.[12] The elevations among firefighters are occurring against a background of a population in which an appreciable fraction use and have used tobacco, especially the older generations of firefighters now retired, retiring, or active but toward the end of their service careers. Their lung cancer risk (as well as the risk of other smoking-related diseases) reflect past patters of tobacco use.

On the other hand, the prevalence of smoking among contemporary fire fighters does not appear to be excessive compared to other "blue collar" occupations.[187 188] 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 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.[188, 189] 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. 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.[3]

Unconfounded 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.[190] However, the empirical findings on lung cancer from recent, well-designed epidemiological studies have been inconsistent.[88] 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[191]. Studies on cohorts from San Francisco[96] and Buffalo[192] showed no excess and even suggest a deficit, as do most of the population monitoring studies (which systematically tend to underestimate risk, and so are not cited in this section). This might be expected if firefighters, on average, smoke less than the general population and there is some evidence for this.[187]

In 1995, we proposed that the true risk for lung cancer associated with fire fighting overall, taking both smokers and nonsmokers together, was probably on the order of 150.[88] We suggested then that the true risk has been underestimated in career fire fighters and both overwhelmed and confounded by the effect of cigarette smoking, which is a much greater risk factor. This figure has been disputed. There are contextual reasons for thinking that the true risk has been underestimated in career firefighters.

Virtually all 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%.[88] The principal exceptions are Baris et al.[18], and Vena and Fiedler[192]. Baris et al.[18], despite a low overall risk (1.13, 95% 0.97 – 1.32) does report suggestive elevations in certain subgroups, notably fire fighters with less than 9 years of service (1.52, 95% CI 1.16 – 2.01), those assigned to engine companies (1.18, 95% CI 0.93 – 1.51), and those hired before 1935 (1.30, 95% CI 0.97 – 1.73).[192] Vena and Fiedler[192] present one of the lower overall risks in the fire fighting literature (0.94, 95% CI 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.[193]) Heyer et al.[180] reported an overall risk of only 97 (95% CI 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.[96] reports the lowest risk (0.84, 95% CI 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 one study by Hansen et al.[191] in which an overall risk of 163 (95% CI 75 – 310) was accompanied by a tripling of risk (317) for firefighters aged 60 to 74. This is an imaginative Danish study that aggregated other occupational groups into a synthetic reference group. The artificiality of this construct makes the study difficult to interpret, however.

In our study of urban fire fighters in Alberta[141], 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.[18], 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.[194] 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. Again, 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.[141] 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.

Taken together, and supported by the methodologically stronger studies in the literature, 150 seems to be a reasonable estimate of the true (unconfounded) risk for lung cancer among firefighters. The attributable risk fraction would therefore be on the order of 50% for firefighting as an occupation. For the average firefighter, therefore, the most likely estimate of the risk associated with working as a firefighter would be about half that of the risk associated with living in the community.

The Non-Smoking Fire fighter

The findings of epidemiological studies are not necessarily applicable to the circumstances of an individual case. Claims under workers' compensation and other adjudication systems are generally required to be based on individual circumstances, not on broad generalizations, unless there is a relevant presumption and no unusual circumstances to rebut it. One of the individual factors of greatest practical importance is smoking.

When lung cancer occurs in a firefighter who does not smoke, the relevant comparison is to the risk of other nonsmokers, not the population as a whole, which includes many smokers. For a non-smoking firefighter, the a priori risk for lung cancer is low. Is the additional risk attributable to fire fighting sufficient to achieve a doubling, the threshold for presumption? There is evidence that it is but some reasonable assumptions are required.

There is no study available that describes the experience of non-smoking firefighters. This is not unusual: it is difficult to identify or to partition out the risk of non-smokers in most epidemiological studies of occupational risk factors. Although lung cancer is rare in people who do not smoke, when it occurs it is usually adenocarcinoma. However, adenocarcinoma is also increased among smokers, so tissue type does not help as an indicator in the individual case.

In calculating the SMR or relative risk, both the numerator and the denominator typically include smokers. Smokers among the firefighters contribute the great majority of cases of lung cancer, as they do in the general population. Although their risk may be increased compared to similar smokers who do not fight fires, the increase is probably small in absolute terms, given their already increased risk from smoking, which is in the range of 5 to 10 times that of nonsmokers.[144] In the 1980's, perhaps 30 to 40% of firefighters smoked; the data available are sketchy but seem to be more or less in line with the general population. [187] The question therefore is how to estimate the relative risk of nonsmoking firefighters when most of the cases are already coming from smokers.

One may assume that, within a reasonable range of exposure, the magnitude of an increase in risk for lung cancer that is associated with a given exposure to combustion products from fighting fires would be the same for smoking and non-smoking fire fighters. This exposure is added to the greatly increased risk sustained by smoking firefighters who receive much more intense exposure to similar and probably more potent carcinogens in cigarette smoke. [2,6] We may therefore assume a model in which the risk of exposure to combustion products from fires and the risk from smoking are roughly additive. For smoking firefighters, the risk arising from work is added onto the existing risk derived from cigarette smoking, which is about ten times the risk of lung cancer experienced by nonsmokers, overall. Thus, if the risk of lung cancer is increased by 50% for smoking firefighters, the proportionate increase in risk for non-smokers would be much greater, by as much as tenfold, because the same attributable risk is added to a much smaller baseline risk. Seen another way, the relative risk will be hugely increased if nonsmoking firefighters are compared to nonsmokers in the general population, because the risk attributable to occupation would be compared to a much smaller baseline risk for the reference population.

One approach to quantifying the risk of nonsmoking firefighters is to estimate that 40% (f = 0.4) of fire fighters smoke (an great overestimate for contemporary firefighters but not unreasonable for firefighters currently retired) and that 60% do not (1 – f), that the relative risk (represented as RR elsewhere in this document) of lung cancer for smokers is 10 times that of nonsmokers

(R = 10.0, where the relative risk of lung cancer for nonsmokers is defined as 1), and that the relative risk of lung cancer for fire fighters overall (r in this equation) is 1.5. If x represents the attributable risk fraction, then:

$0.4(10+x) + 0.6(1+x)/0.4(10) + 0.6(1.0) = 1.5$

Solving for x yields an attributable risk fraction of 2.3. This translates to a relative risk for nonsmoking fire fighters of 3.3, comfortably above a doubling. The exact value is unimportant because of the compounded uncertainties; that it exceeds a doubling is what matters.

Another way to approach the problem is to determine, based on the same assumptions, what the minimum relative risk for the firefighters as a whole would have to be to reflect a true doubling of risk for nonsmoking firefighters. The calculations are similar and yield r = 1.22, which is comfortably supported by the world literature (whether or not the true risk is 1.5, as has been argued above). How sensitive is this model to underlying assumptions? Reducing the estimate of the proportion of the firefighting population that smokes to 30% barely changes the overall relative risk required to support the presumption, to 1.27. Reducing the estimate of the relative risk associated with smoking from 10 to 5, which is a low estimate and which intentionally biases the model against nonsmokers, increases the overall relative risk required to support the presumption to 1.38, still in line with the world literature and below the 1.5 level that probably represents the "true" risk. Again, the exact number is unimportant; what matters is that the overall risks that would be associated with a doubling in the subgroup of nonsmoking fire- fighters falls into an area entirely consistent with the literature and therefore best evidence.

However, the most relevant comparison of all is a simple ratio to the nonsmoking population using the attributable risk function defined above. If a nonsmoking firefighter were compared to a similar population of people who also do not smoke, the expression would be:

$0.6(1 + x)/0.6(1.0) = 1 + x = 3.3$

which is the relative risk given above. (This is not coincidence, just the result of a mathematical identity. The group risk of people who do not smoke is defined as unity.)

The importance of these analyses is that they demonstrate by robust means that the risk is clearly elevated and above the level that would support a presumption. These figures should not be taken as exact estimates of the true risk of lung cancer among nonsmoking firefighters. There are too many inherent uncertainties for these estimates to be accurate. To be sure it is important to allow a large margin for error. That is why it is important that the end result of the analyses do show that the relative risk for nonsmoking firefighters is substantially greater than a doubling.

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. The exact value is unimportant because of the compounded uncertainties; that it clearly exceeds a doubling is what matters most. Thus, it seems apparent that the available evidence supports the conclusion that the risk for lung cancer among nonsmoking firefighters is at least doubled compared to the general nonsmoking population.

COLON CANCER

There may now be sufficient evidence to consider colon cancer for a presumption. 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". Recent studies, including thorough and detailed work of high quality such as Baris et al.[18], 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).

Overall, Baris et al. found an SMR of 1.51 (95% CI 1.18, 1.93), based on 64 deaths; there was no consistent dose-response for duration of employment or for cumulative number of runs. 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[195] and Vena and Fiedler reported a significantly elevated SMR of 1.83. Thus, two studies, one in two out of three subgroups and the other in the population as a whole, have demonstrated relative risks close or equal to a doubling. 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. (We have put this forward in the case of a young vegan with no family history of the disease or of polyps, but the claim was not accepted.)

Kang[134], using a methodology that tends to underestimate risk, observed a statistically significant excess when compared to police (SMOR=1.36, 95% CI = 1.04-1.79) but not another referent population (SMOR=1.15, 95% CI = 0.93-1.43).

Ahn et al.[135] 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, 95%CI = 1.07.1.67).

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. However, this is not valid. 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 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 also 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 and behaviour. Colon and rectal cancer is therefore the same disease, appearing at different locations in the gastrointestinal tract.

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

THYROID CANCER

Thyroid cancer is a relatively uncommon cancer that is easily treated and seldom fatal. It is therefore not usually observed in mortality studies. There is no obvious exposure 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.

The study by Ma et al.[60, 124] of Florida firefighters contained the striking observation that cancer of the thyroid is markedly and statistically significantly elevated for both male and female firefighters (SIR=1.77, 95% CI = 1.08-2.73; 3.97, 1.45-8.65). As yet, these findings have not been duplicated. Thyroid cancer appears in this study and not others presumably because Ma et al.[60, 124] is a cancer incidence study) rather than the more common mortality study. Kang (2008) in the study of Massachusetts firefighters, did not observe an excess but that study had much less power.

Thyroid cancer might be affected by screening bias favoring detection of cases in individuals with better health care, since it is possible to have thyroid cancer and not know it.

As yet, there is insufficient evidence to make a recommendation but if future studies demonstrate an elevation of similar magnitude, a presumption may be justified for thyroid cancer on the basis of consistency and the strength of the association, despite the absence of a putative mechanism or known responsible exposure.

OTHER CANCER TYPES

Elevations in risk have been found in other cancer types but so far without confirmation or replication.

Bates[133] demonstrated a statistically significant elevation for melanoma among California firefighters (OR=1.50, 95% CI = 1.33-1.70). The most plausible exposure responsible for this would be ultraviolet radiation, 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.[30]

Bates[133] also demonstrated a statistically significant elevation for esophageal cancer among California firefighters (OR=1.48, 95% CI = 1.14-1.91). 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 known risk factors for esophageal cancer include esophageal reflux disease (Barrett's esophagus), alcohol intake, smoking, and obesity. 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. At present this isolated finding cannot be adequately evaluated.

Firth[138, 196] found an astronomical elevation in risk for cancer of the larynx (SIR, expressed as a percentage=1348, 95% CI = 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.

CONCLUSION AND RECOMMENDATIONS

Based on the weight of evidence presented above, we recommend the following:

GENERAL

The experience with firefighters suggests that it is reasonable to approach knotty adjudication problems by framing the question differently and using collateral evidence to interpret the epidemiological findings. This is particularly true when the purpose is application of epidemiological findings to a legal or adjudication process. When a strong potential exists for misclassification or dilution of risk estimates, or when power considerations make the achievement of statistical significance unlikely because of small numbers, elevated risks take on added significance.

CARDIOVASCULAR DISEASE

The extant evidence clearly demonstrates that firefighters are at an increased risk of cardiac events ("heart attacks") but it is not clear that firefighting, in itself, causes cardiovascular disease. The current guidelines of the National Fire Prevention Association consider a heart attack to have been in the line of duty when symptoms begin within 24 hours of an alarm. Available evidence suggests that this is reasonable and even conservative.

We recommend that future studies of cardiovascular risk factors among firefighters go beyond prevalence whenever possible and try to reconstruct cohort trends, in order to clarify the current, undoubtedly mixed picture of the distribution of risk in this occupation. Whenever possible, data should be adjusted by age, for fire department policies on fitness, and for volunteer or career status of firefighters.

Facilities and policies encouraging firefighters to work out with exercise while on duty are associated with greater compliance with exercise routines and are likely to lead to better outcomes and lower risks. They are therefore to be encouraged among fire departments as an investment public services.

Hypertension is widely unrecognized and undertreated among firefighters. A concerted program of aggressive control of blood pressure among emergency responders is a priority for management of this population.[116]

CANCER

In this analysis we have placed greatest weight on the magnitude and consistency of the association for bladder and kidney cancer, which are discreet and separable tumours, and on suggestions of an elevation in various subgroups for brain, lymphatic (non-Hodgkin's lymphomas) and haematopoietic cancers.

The weight of evidence to date suggests that the elevation in risk for brain cancer reflects a true risk in certain subgroups, as demonstrated in black firefighters, but these subgroups cannot be readily identified by usable criteria in adjudication. The inconsistency in the literature cannot be explained by current data but given power considerations, the demonstration of an excess in past studies appears more convincing as evidence of a confounded or obscured association than the inconsistency is convincing as evidence of no association.

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. The more recent evidence is consistent with an elevation for lymphoma and does not contradict the finding in other studies of an increased risk for haematopoietic cancers (leukemias). The L'Abbe and Thomlinson[21] and Demers et al. [179] studies, for example, provide strong evidence suggesting an elevated risk notwithstanding the variation in risk estimates in other studies. Baris et al.[18] present a confusing picture for non-Hodgkin's lymphoma because employment for 20 or more years produces and SMR of 1.72, with elevated risk for those hired after 1935, but there was an inverse of risk for cumulative number of runs. Thus, the earlier recommendations from the IDSP[204], and by Guidotti[88], for an implied presumption but with individual evaluation of each case, are not contradicted by the new evidence.

The evidence available since 1994 suggests that it is reasonable given the available scientific evidence to adopt a policy of presumption for brain cancer, bladder cancer, kidney cancer, non-Hodgkin's lymphoma (lymphatic cancer) and leukemia (haematopoietic cancer) for claims associated with occupation as a firefighter. The presumption for brain cancer, bladder cancer and kidney cancer are based firmly on a strong suggestion of an excess in the literature. The presumption for non-Hodgkin's lymphomas and leukemias are based on the inference that within the overall category there are specific disorders for which the evidence suggests an elevated risk but it is not possible to discern which among several are in excess. A presumption for lung cancer in firefighters who do not smoke is based on the premise that the carcinogenic potential of cigarette smoke and other products of combustion are probably comparable and the risk estimates can therefore be manipulated to "subtract" out the background of smokers' risk.

The risk of colon cancer does not rise to a level where a presumption can be confidently defended. There is a clear although not high elevation but the extent to which this is associated with the occupation of firefighting, with nutrition and lifestyle factors associated with employment in firefighting, or with a slightly background risk of colon cancer in the subpopulations from which firefighters are recruited is unclear. In the past, we have only made the case for such claims when (and only when) the background risk level assumed for the individual was unusually low (because of vegan diet and athletic levels of exercise), on the grounds that this should have been protective. (Evaluation of individual claims requires individual evaluation; the best available estimate of personal risk, however, is usually the population estimate for the subgroup to which the individual belongs.) Adoption of a presumption, based on what is known at this time, would probably include more claimants for whom their occupation played little or no role than claimants for whom their risk arose out of work. It is a policy decision as to whether this is acceptable.

Melanoma risk most probably depends on exposure to ultraviolet light out of doors, although some melanoma arises from other causes. No general causation strong enough to support a presumption can be established and so cases should be evaluated individually.

The risk of thyroid cancer is a new and unexpected finding supported by strong evidence from one study. [60] The older but isolated observation for esophageal cancer also rests on a single study.[196] This may be an instance of the classic "first case" problem, in which new findings in the recent literature always place a claimant for a newly-discovered disorder at a disadvantage, because the evidentiary base is always incomplete. These cases are usually denied. Without a mechanism to review and return to closed cases, they may not be fairly compensated even after an association is confirmed and recognized. On the other hand, these elevations might reflect causation. The totality of evidence at this point is insufficient to determine the weight of the evidence.

Prostate cancer is a complicated problem but there are compelling reasons to believe that elevations for particular groups, including firefighters, represents screening bias and not causation. No presumption is recommended for prostate cancer.

Table 3 summarizes these recommendations.

The application of epidemiology to adjudication and litigation is based on a different set of rules than for scientific investigation. The role of the expert is to give guidance as to the weight of the evidence, not to produce more data or to determine revealed truth through the scientific method. This is particularly important in addressing an individual claim, when generalities based on population data are no longer necessarily valid. As our data resources become more constrained and in many cases outdated, it will become increasingly necessary to interpret the data with greater understanding of the problem rather than relying on rules designed for other purposes, such as the Hill criteria.

Table 5. Summary of Recommendations.

Conditions for Which a Presumption is Justified by Current Evidence

- Heart attacks following soon after an alarm or event (up to 24 to 72 hours)
- Bladder cancer
- Kidney cancer
- Testicular cancer
- Lung cancer in a non-smoking firefighter
- Non-Hodgkin's lymphomas (Current knowledge precludes differentiating by type)
- Myelomas (Current knowledge precludes differentiating by type)

Conditions for Which a Presumption is Justified with Qualification

- Brain cancers (Glioma is more likely than other types to be related to work)
- Leukemias (Acute myeloid leukemia most likely)

Conditions for Which an Association is Suggested by Current Evidence

- Lung cancer (Rebuttable based on smoking history)
- Colon cancer
- Melanoma (For firefighters who mostly work outdoors, such as wildfire fighters)

Conditions Requiring Further Evaluation (Insufficient Evidence)

- Thyroid cancer

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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. 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 and implementation of a multicentre study of firefighters currently in the initiation phase by the National Institute of Occupational Safety and Health (US).

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). He is a Canadian citizen (dual with US citizenship) and holds an adjunct faculty appointment at the University of Alberta (Centre for Advanced Business Research in Energy and Environment). He 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 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).

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. He 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*

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