

REVIEW OF THE REPORT OF CANCER CARE ONTARIO ON OCCUPATION OF FIREFIGHTING AND CANCER RISK

Submitted to the Worker's Compensation Board of British Columbia by Drs Pierre Band and David Parker, October 4th, 2004.

The Workers' Compensation Board of British Columbia Corporate Supply Management, hereafter referred to as the WCB entered into an agreement with Drs. Pierre Band and David Parker to provide the WCB with an independent critical review of the following report:

Title: The Occupation of Firefighting and Cancer Risk: Assessment of the Literature

Date: June 15, 2004

Submitted by: Ruhee Chaudhry
Loraine Marrett
Nancy Kreiger
Terry Sullivan

Affiliation Division of Preventive Oncology, Cancer Care Ontario (CCO)

It was stipulated that this critical review should be written jointly by Drs. Band and Parker and that areas of agreement and if present, areas of disagreement, be indicated. In this report, areas of disagreement will be indicated; when no such specific mention is made, it should be understood that both reviewers are in agreement with the statements made.

In this review, specific comments will be addressed in the order of the headings used by CCO in their report. Before doing so a minor point needs to be made: the CCO report, dated June 15, 2004, has 2 pages numbered 4. This will need to be corrected in the final report.

1.0 Background

Overall, the authors' review on firefighter's exposure although good is incomplete. There is minimal discussion of the possible relationship between mortality, cancer and environmental exposure. While not all studies may show a positive relationship between a specific cancer or group of malignancies, several studies indicating a possible relationship are rendered more credible by a careful review of potential or known exposure. The United States National Institute for Occupational Safety and Health (NIOSH) has recently published a review of studies examining potential hazardous exposures to firefighters (NIOSH, 2004). No reference to this report was found.

Several factors are of importance to the review of malignancies and fire fighters that are discussed in the NIOSH report: (1) Fire fighters face a broad scope of potential exposures; (2) Among others, these exposures include benzene, diesel exhaust, and polycyclic aromatic hydrocarbons (PAC's); and (3) Exposures will vary greatly and with time. While the authors of the report discuss issues such as smoking and bladder cancer, they fail to substantively consider the possible relationships between other exposures and the malignancies of interest. This discussion is necessary in order to assure that adequate weight is given to all of the Bradford-Hill criteria.

2.0 Objectives

The objectives are clearly stated. However, there are several limitations:

1. The reasons for limiting the review to 10 cancer sites and excluding other sites are not specified and should be justified.

2. Limiting the review to lung cancer in non-smokers cannot be justified. In addition, this objective is close to be impossible given the difficulty inherent in finding studies that control for smoking, job exposure, and other confounding variables.

3. Specific subtypes of leukemia should be included in the review.

4. In the results section, data has been presented on rectal cancer and lung cancer (not limited to non-smokers); the results section makes no mention of urethral cancer which is included under “objectives”. The section on objectives should be redrafted to reflect these modifications.

3.0 Methods

3.1 *Systematic literature search and data sources*: Although the literature search is reasonably comprehensive and well described, it may have been useful for the authors to have conducted searches of Toxline and on a broader range of keywords such as mortality, standardized mortality, and epidemiology, as well as on specific malignancies to ensure that materials have not been missed. This is particularly true with regard to the evaluation of exposure to firefighters.

The authors present a series of numbers in Table 2. The meaning of these numbers is unclear. The authors use some terminology that is uncommon and should be avoided. For example, the table (and text) states, “Occupational Exposures –exploded.” Both reviewers are unfamiliar with this terminology and the use of reference jargon should be avoided. While it is reasonable to include all English language studies, the authors do not comment if studies are available in other languages. It would have been useful to at least consider those studies having an abstract written in English and comment on whether or not inclusions of these studies might have contributed to the analysis and/or modified the conclusions

3.2 *Inclusion and exclusion criteria*: This section does not clarify how many studies were excluded for reasons other than being surveillance or PMR studies or overlapping population(s). More information should be presented on study exclusion and how these studies might potentially modify conclusions. It would have been useful to have a summary of the findings of the studies that have been excluded.

The studies summarized in Appendix B but not considered for analyses by the authors of the CCO report ought to have been analyzed the same way the authors have done for the cancer sites listed in section 2.0 (Objectives), at least for the specific organ sites. There needs to be a discussion on how duration of employment was used in different studies; this is one of the most critical variables in any occupational study.

➤ **Reasons for including and excluding studies are a cause of discrepancies between the reviewers and COC and between the reviewers themselves. This issue will be addressed under section 3.4.**

The decision made by CCO to exclude occupational surveillance and PMR studies appears arbitrary and questionable.

3.3 *Data extraction*: This section represents a reasonably comprehensive overview of extracted variables. It would have been helpful to have a more clear definition of several issues: (1) how was exposure evaluated? The authors note a variable called exposure definitions. However, this does not inform the reader if the paper is describing years at risk or

latency. (2) The variable, “adjustments to main analysis” is unclear in its meaning. (3) The term “effect measure” is unclear in the context of this analysis.

3.4 *Quality Assessment*: While it is reasonable to randomly assign manuscripts to reviewers, there should be a clear description of who the reviewers were and how there was an assurance that quality was similarly assessed between reviewers. The manuscript goes on to note, “Through this process 14 studies were classified as weak for various reasons and 18 as adequate or good.” Table 4 provides reasons for these exclusions. This table requires clarification and more explanation of each exclusion criteria.

While there are clear limitations to proportional mortality studies, these limitations are outweighed by their strengths. This is especially true in the absence of a clear indication of bias in the population being studied. A listing of proportionate mortality studies that were excluded should be provided. These studies should be included in the review or there should be an explanation as to how their inclusion might have modified the final conclusions.

The report states, “While surveillance studies of this type can provide valuable information for hypothesis generation and identifying areas for further study, they are not strong designs for the purpose of assessing cancer risk.” The results of surveillance studies may add to conclusions, may point to risks that have been explained by others, and may provide information on exposure that is not reported in other work. Surveillance data should be included if it is able to clarify potential work-exposure relationships.

➤ **Discrepancies between CCO and the reviewers and between reviewers concerning study inclusion and exclusion.**

As indicated above, study inclusion and exclusion represents a cause of discrepancies: Table 1 summarizes the agreements and disagreements in assessment.

Correspondence between one of the reviewer (PB) in assessing the studies included and excluded by CCO:

1. Studies excluded by both CCO and PB: Brownson, Deschamps, Feuer, Figgs, Krstev (mortality), Lewis, Ma, Mastromatteo, Morton, Muscat, Sama, Zahm.

Reviewer’s (PB) reasons for exclusion

Brownson: No information on usual occupation in over one-third of the cases and controls; occupational information based on hospital records. Previous study on correspondence between occupational history obtained on interview and from medical charts was 70%. Hence, about 45% of studied cases and controls would have accurate occupational information (70% of 66%).

Deschamps: Except for 2 cases of pharyngeal cancer, no data on other specific cancer sites.

Feuer: Multiple controls with different results for the same cancer site.

Figgs: Excludes cancer cases from the control group (controls not representative of the overall population). Data reported for firefighting supervisors (12/602 = 2% white males in service occupations) whereas service occupations account for 602/11246 = 5% of white male deaths. There are likely more firefighters than firefighting supervisors among the 602 service occupations, but the paper makes no mention of this possibility.

Krstey: (death certificate): Excludes cancer cases from the control group (controls not representative of the overall population).

Lewis: Data broken down by age groups; age groups not consistent; no statistics.

Ma: Excludes cancer cases from the control group (controls not representative of the overall population).

Mastromatteo: 20% lost to follow-up. No data on specific cancer sites.

Morton: Occupational data abstracted from hospital medical records; proportion of total missing occupational information not clearly stated. However, the proportion of “unemployed or not in the work force” is 27% for all men but 58% for the leukemia cases (Table II). Leukemia cases among protective services in all men are reported to be 6 in table VII but 11 in Table XIII.

Muscat: Hospital-based study.

Sama: Occupational data derived from hospital records and available on only 50% of the cases.

Zahm: Occupational data abstracted from medial records; unknown occupational information on 2107/4431 (48%); includes police + protective services with firemen.

2. Studies excluded by CCO but included by PB: Burnett, Firth, Grimes.

Reviewer’s (PB) reasons for inclusion

Burnett: Unbiased study: controls include all deaths, cancer and non-cancer causes.

Firth: Cancer incidence study reporting 4 cases of laryngeal cancer (statistically significant) among firefighters (data in the text, not in the Tables).

Grimes: Unbiased study with data for Caucasians.

3. Studies included by CCO but excluded by PB: Delahunt, Hansen, Stang

Reviewer’s (PB) reasons for exclusion

Delahunt: Firefighters are included with “service occupations”; number of firefighters not stated. Relative risks estimates varies: 4.89 in the abstract, 4.69 in the text, 3.51 in the Table.

Hansen: Controls “hand picked”: not representative of the general population.

Stang: Strong likelihood of “selection and ruminant bias” i.e., controls interviewed 57% versus cases interviewed 78%.

Correspondence between one of the reviewers (DP) in assessing the studies included and excluded by CCO:

1. Studies excluded by both CCO and DP: Brownson, Deschamps, Mastromatteo, Zahm

Reviewer's (DP) reasons for exclusion

Brownson: The paper notes exclusion of 34% of potential cases and 38% of potential controls. I agree this is a large percent; however, is there any indication that it is biased in any direction? I am neutral about the inclusion of this manuscript apart from the fact there are few studies on brain cancer to include.

Deschamps: This manuscript has limited data.

Mastromatteo: An interesting paper from an historical view but of little utility.

Zahm: This manuscript provides little useful information because of a lack of detail

1. Studies excluded by CCO but included by DP: Burnett, Feuer, Figgs, Firth, Grimes, Morton, Muscat, and Sama.

Reviewer's (DP) reasons for inclusion

Burnett: There is no reason to exclude this study. There is no evidence that this PMR is biased.

Feuer: While the results in Table II and IV are a bit different their direction is the same. I do not see a reason to exclude this study.

Figgs: This is a large population-based study. While death certificate studies suffer several weaknesses there do not appear to be any factors that inherently bias this study. While I think it ought to be considered in the final report, its exclusion would not be a significant loss.

Firth: There is no reason to exclude this study. There is no evidence of bias and it appears to have been properly done.

Morton: I find Table II very confusing. It is unclear to me what the authors mean by the product labeled N_p . It does not appear to be a percent of cases without occupation. However, it appears in Table XIII that the measures are highly significant statistically and the cases are broken down (to a limited degree) by leukemia type. Although the case number is small, I do not find this overly troubling. Also, Table VIII appears to be women. Overall, it appears that the strengths of this study outweigh its weakness.

Muscat: I do not find a good reason to believe the results were biased. However, the differences in exposure rates between cases and controls were small. Exposure seems to have been poorly defined. Exclusion of this study is neither recommended nor encouraged.

Sama: The selection of firefighter cases appears to have been reasonably done (see page 49, paragraphs 1 and 2). Although the percent of cases without occupation is high, there is no reason to believe that this has introduced a bias in any direction. The authors note this may underestimate risk to firefighters. This study ought to be included.

2. Studies included by CCO but excluded by DP: Delahunt

Delahunt: No good data on firefighters.

Correspondence between both reviewers in assessing studies included and excluded:

1. Studies excluded by both reviewers: Brownson, Delahunt, Deschamps, Mastromatteo, Zahm.
2. Studies excluded by PB, included by DP: Feuer, Figgs, Lewis, Ma, Muscat, Sama, Stang, Hansen.
3. Studies excluded by DP, included by PB: none

TABLE 1: Studies included, excluded and considered (consid) by Cancer Care Ontario (CCO) and by the reviewers, Pierre Band (PB) and David Parker (DP), in their respective evaluation.

STUDIES	TYPE	CCO	PB	DP
1. Aronson		Included	Included	Included
2. Baris		Included	Included	Included
3. Bates	SMR	Included	Included	Included
4. Bates	SIR	Included	Included	Included
5. Beaumont		Included	Included	Included
6. Brownson		Excluded	Excluded	Excluded
7. Burnett		Excluded	Included	Included
8. Delahunt		Included	Excluded	Excluded
9. Deschamps		Excluded	Excluded	Excluded
10. Demers '92		Included	Included	Included
11. Demers '93		Included	Included	Included
12. Demers '94		Included	Included	Included
13. Eliopoulos		Included	Included	Included
14. Feuer		Excluded	Excluded	Included
15. Figgs		Excluded	Excluded	Included
16. Firth		Excluded	Included	Included
17. Gallagher		Not consid	Consid	<i>Not seen</i>
18. Giles		Included	Included	Included
19. Grimes		Excluded	Included	Included
20. Guidotti		Included	Included	Included
21. Hansen		Included	Excluded	Included
22. Krstev	Deaths certificate	Exclude	Excluded	<i>Not seen</i>
23. Krstev	Incidence	Included	Included	Included
24. Krishnan		Included	Included	Included
25. Le		Not consid	Consid	<i>Not seen</i>
26. Lewis		Excluded	Excluded	Excluded
27. Ma		Excluded	Excluded	Included
28. Mastromateo		Excluded	Excluded	Excluded

29. Morton	Excluded	Excluded	Included
30. Muscat	Excluded	Excluded	Included
31. Musk	Included	Included	Included
32. Sama	Excluded	Excluded	Included
33. Stang	Included	Excluded	Included
34. Tornling	Included	Included	Included
35. Vena	Included	Included	Included
36. Zahm	Excluded	Excluded	Excluded

3.5 *Analysis*: Accepted methods for statistical and meta-analysis are used. The rationale for not calculating summary estimates for cancer sites with two studies is arbitrary: some cancer sites with two studies may have observed number of cases greater than those of the majority of studies with three or more cases. For instance, for bladder cancer, the observed number of incident cases, 23, is greater than the sum observed in 5 out of the 7 mortality studies.

A problematic issue posed by the researchers is the use of follow-up cohorts in deference to earlier studies using the same cohort. This appears to be the most logical course to pursue; however, this practice has been drawn into question (see Silver et al., 2002); these authors (Silver et al.), citing Lamm et al (1989), note that in fact the time since last exposure may be more important than time since first exposure if risk of disease decreases with time, indicating that a substance might act as a tumor promoter. The report should reflect the work of these authors and account for other types of statistical modeling with regard to tumor development (i.e., the last is not necessarily the best study). As an example, the risk of lung cancer decreases during the time period after a person stops smoking.

3.6 *Criteria for Conclusion*: On page 10, a list of criteria from which conclusions are derived is actually based on the set of criteria shown on Table 5 (page 11). While the listed criteria appear reasonable, those presented in Table 5 for limited and sufficient evidence is arguable. Particularly, “at least one substance to which firefighters may be exposed at work is carcinogenic for this cancer site” is too restrictive taking into account the limited knowledge on cancer site specific carcinogens. Also, “evidence of a dose-response relationship” is too vague: is it for all studies, for at least one of them, for over half of them? What would be the conclusion for studies with only pooled estimates being significant?

4. Findings

A. Assessment of CCO’s report by reviewer PB

In assessing the CCO’s report, reviewer PB has considered: a) the results of the cancer sites as evaluated in the CCO report; b) the results of the studies which this reviewer included and considered; c) the results of re-analyzing the data as follows: summing up observed cases and expected numbers to obtain pooled estimates of SIRs, SMRs and PMRs and calculating 95% confidence intervals around these pooled estimates using the software Stata (Stata Corporation, College Station, Texas, USA); d) risk factors criteria, categorized into established, probable and possible, according to the definitions of the Harvard Center for risk Analysis (Rhomberg L, Kang JH) as follows: established risk factors are those well corroborated; probable factors are “those for which more studies show the effect than not, but the findings are not felt to be certain because of some contradictions or the inability to rule out with confidence alternative explanations”; possible factors are “those for which some positive results exist, but these findings have not generally been corroborated and significant questions remain about whether there is any effect.”

Based on these criteria, the following three categories were derived to reach conclusions on the potential cancer risk associated with the occupation of firefighting:

Categories: Pooled estimates of incidence (I), mortality (M) and PMR (P) significant (+) or not significant (-)

- | | |
|--------------------------|--|
| 1. Insufficient evidence | I ⁻ M ⁻ P ⁻
I ⁻ M ⁻ P ⁺
I ⁺ M ⁺ P ⁻ |
| 2. Possible cancer risk | I ⁺ M ⁺ P ⁺
I ⁺ M ⁻ P ⁺
I ⁺ M ⁺ P ⁻ |
| 3. Probable cancer risk | I ⁺ M ⁺ P ⁺
I ⁺ M ⁺ P ⁻ |

In addition the Bradford Hill criteria have been considered in supporting or not the evidence for a possible or probable cancer risk

4.1 *Bladder cancer*: The summary of the studies reviewed by CCO as described in the first two paragraphs are accurate. The total number of observed cases and expected controls and this reviewer's summary risk measures for the 2 incidence and 7 mortality studies reported in Figure 1 (page 13) and the 95% confidence intervals (95% CI) are:

Incidence 23/19.68 = 1.17 (95% CI 0.74-1.75)
Mortality 46/41.75 = 1.10 (95% CI 0.81-1.47)

In addition 3 studies, the 3 PMR studies of Burnett, Gallagher and Le, reporting on bladder cancer in firefighters have been excluded by CCO; the summary for these studies is:

PMR 53/46.26 = 1.15 (95% CI 0.86-1.50)

Conclusion: The results of the 2 incidence studies are consistent with each other showing a modest increased risk with pooled estimate of 1.17; results of the mortality studies, though less consistent, showed a pooled estimate of 1.10; data from the 3 PMR studies not considered by CCO had a summary estimate in the same range.

➤ Overall, these results are insufficient to determine whether bladder cancer is a risk associated with the occupation of firefighting.

4.2 *Brain and nervous system cancers*: The summary of the studies reviewed by CCO as described in the first two paragraphs are accurate. However, it should be noted that the study of Krishnan reports data for usual as well as ever occupations. In the CCO report, only the information on ever firefighter is considered (OR = 2.85). The OR for usual occupation as firefighter is 5.88 (95% CI 0.70-49.01). The total number of observed cases and expected controls and this reviewer's summary risk measure for the 4 incidence and 9 mortality studies reported in Figure 2 (page 15) and 95% CI are:

Incidence with case control study 23/14.20 = 1.62 (95% CI 1.03-2.43)
Incidence without case control study 14/11.20 = 1.25 (95% CI 0.68-2.10)
Incidence with usual occupation 20/12.20 = 1.63 (95% CI 1.00-2.53)

Mortality 73/53.32 = 1.37 (95% CI 1.07-1.72)

In addition 3 studies reporting on brain and CNS cancer in firefighters have been excluded by CCO: the 3 PMR studies of Burnett, Gallagher and Le; the summary for these studies is:

PMR 51/45.22 = 1.12 (95% CI 0.84-1.48)

Conclusion: Overall, the incidence studies showed a moderate increased risk with attributable risk of up to 47%. The mortality studies have an attributable risk of 27%. Two of the mortality studies showed a statistically significant excess risk and three were suggestive

of an increased risk with employment duration. The three PMR studies not considered in the CCO report revealed a small excess risk with an attributable risk of 11%. Re-analyses of the incidence and mortality studies considered by this reviewer showed significantly increased risks.

Overall, these results are indicative of a probable increased risk of brain and central nervous cancer associated with the occupation of firefighting.

This conclusion is further substantiated by the Bradford Hill criteria of “biological plausibility”, since firefighters are exposed to vinyl chloride which has been associated with a risk of brain cancer. In addition, exposure to coal, oil, petrochemical compounds and rubber also carry a risk of brain cancer; it is likely that exposure to combustion products of these compounds are also associated with a brain cancer risk.

4.3 *Colorectal cancer*: Pooling colon and rectal cancers because of the potential for misclassification is legitimate. The summary of the studies reviewed by CCO as described in the first three paragraphs are accurate. The total number of observed cases and expected controls and this reviewer’s summary risk measure for the 4 incidence and 9 mortality studies reported in Figure 3 (page 17) and 95% CI are:

Incidence $78/73.36 = 1.06$ (95% CI 0.84-1.33)
Mortality $236/180.3 = 1.31$ (95% CI 1.15-1.49)

In addition 3 studies reporting on colorectal cancer in firefighters have been excluded by CCO: the 3 PMR studies of Burnett, Gallagher and Le; the summary for these studies is:

PMR $37/32.61 = 1.35$ (95% CI 0.80-1.56)

Conclusion: Overall, the incidence studies showed no increased risk, whereas the mortality studies revealed a significantly increased risk. In two of the mortality studies the excess risk was statistically significant. The PMR studies revealed a moderate excess with an attributable risk of about 25%.

- Overall these results are insufficient to determine whether colorectal cancer is a risk associated with the occupation of firefighting.

Colon cancer: The summary of the studies reviewed by CCO as described in the first two paragraphs are accurate. The total number of observed cases and expected controls and this reviewer’s summary risk measure for the 3 incidence and 7 mortality studies reported in Figure 3a (page 18) *to which the mortality study of Grimes was added (O/E = 1/1.4; risk ratio 0.71; 95% CI 0.1-5.0)* and 95% CI are:

Incidence $38/41.70 = 0.91$ (95% CI 0.65-1.25)
Mortality $152/135.29 = 1.12$ (95% CI 0.95-1.32)

In addition 3 studies reporting on colon cancer in firefighters have been excluded by CCO: the 3 PMR studies of Burnett, Gallagher and Le; the summary for these studies is:

PMR $22/22 = 1.00$ (95% CI 0.63-1.51)

Conclusion: Overall the incidence studies showed a risk deficit and the mortality studies a small excess with an attributable risk of 11%. Two of the mortality studies with a significant excess, also showed a significantly increased risk associated with employment duration of 20 or more years (Baris) and 40 years and over (Vena).

- These studies taken together provide insufficient evidence for an increased risk of colon cancer in firefighters

Rectal cancer: The summary of the studies reviewed by CCO as described in the first two paragraphs are accurate. The total number of observed cases and expected controls and this reviewer's summary risk measure for the 3 incidence and 7 mortality studies reported in Figure 3b (page 19) and 95% CI are:

Incidence $31/25.5 = 1.21$ (95% CI 0.83-1.73)
Mortality $67/49.24 = 1.36$ (95% CI 1.04-1.73)

In addition 3 studies reporting on bladder cancer in firefighters have been excluded by CCO: the 3 PMR studies of Burnett, Gallagher and Le; the summary for these studies is:

PMR $52/37.61 = 1.38$ (1.03-1.81)

Conclusion: Overall, the incidence and mortality studies showed a small to moderate excess risk with attributable risks of 17.4% and 26 % respectively. The PMR studies had an attributable risk of 27.5% and one of them (Burnett) was statistically significant. Re-analyses of the mortality and PMR studies considered by this reviewer showed a significant excess

- These studies taken together provide evidence for a possible increased risk of rectal cancer associated with the occupation of firefighting.

This conclusion, however, is not substantiated by the Bradford Hill criteria of "biological plausibility", as information on associations between exposures and rectal cancer risk is insufficient. In particular, the study of Siemiatycki did not show a relationship between working as a firefighter and a risk of rectal cancer.

4.4 *Kidney cancer*: The summary of the studies reviewed by CCO as described in the first two paragraphs are accurate. The total number of observed cases and expected controls and the reviewer's summary risk measures for 3 incidence (Delahunt excluded) and 7 mortality studies reported in Figure 4 (page 21) and 95% CI are:

Incidence $7/14 = 0.48$ (95% CI 0.19-0.99)
Mortality $34/32.67 = 1.04$ (95% CI 0.72-1.46)

In addition 2 studies reporting on kidney cancer in firefighters have been excluded by CCO: the 2 PMR studies of Burnett and Gallagher; the summary for these studies is:

PMR $56/41.09 = 1.36$ (1.03-1.77)

Conclusion: There is no evidence of an increased risk from the incidence and mortality studies. Attributable risks for the 2 pooled PMR studies is 26.47%. One of the PMR study (Burnett) was statistically significant (53 observed cases and 36.81 expected, PMR 1.44, 95% CI (1.08, 1.89), attributable risk 31%), whereas the study of Gallagher had 3 cases observed and 4.28 expected.

- Overall, the information available provides insufficient evidence of an increased risk of kidney cancer associated with the occupation of firefighter.

4.5 *Leukemia*: The summary of the studies reviewed by CCO reported in Figure 5 (page 23) does not consider the study of Aronson that includes 8 cases of leukemia (4 lymphatic and 4 myeloid). The total number of observed cases and expected controls and the reviewer's summary risk measures for the 2 incidence and 4 mortality studies (including Aronson) and 95% CI is:

Incidence $6/6.2 = 1.00$ (95% CI 0.36-2.11)
Mortality $44/45.14 = 0.96$ (95% CI 0.71-1.31)

In addition 3 studies reporting on leukemia in firefighters have been excluded by CCO: the 3 PMR studies of Burnett and Gallagher; the summary for these studies is:

PMR $71/60.73 = 1.27$ (95% CI 0.91-1.48)

One of the mortality studies (Demers) showed a significantly increased risk with employment duration of 40 years and over, and one of the PMR studies indicated a significantly increased risk of leukemia for firefighters less than 65 years of age based on 33 observed cases, 19.29 expected for a PMR of 1.71 (95% CI 1.18-2.40).

Conclusion: Overall, there is no evidence of an increased risk from the incidence and mortality studies. Attributable risks for the 3 pooled PMR studies is 21.3%. One of the PMR study (Burnett) was statistically significant (33 observed cases, 19.29 expected, PMR 1.71, 95% CI (1.18, 2.40), attributable risk 41.5%), whereas the study of Gallagher had 3 cases observed and 4.28 expected. With the exception of Aronson, all studies reported on all leukemia combined (one including aleukemia) and only one (Aronson) had information specific to leukemia sub-types, particularly acute myelocytic leukemia known to be associated with benzene exposure.

- Overall, these results are insufficient to determine whether leukemia is a risk associated with the occupation of firefighting.

4.6 Lung cancer: The summary of the studies reviewed by CCO as described in the first two paragraphs are accurate. The total number of observed cases and expected controls and this reviewer's summary risk measures for 4 incidence and 7 mortality studies (this reviewer excluded the study of Hansen) reported in Figure 6 (page 25) and 95% CI are:

Incidence $84/87.49 = 0.96$ (95% CI 0.77-1.19)
Mortality $423/419.57 = 1.01$ (95% CI 0.91-1.11)

In addition 3 studies reporting on leukemia in firefighters have been excluded by CCO: the 3 PMR studies of Burnett and Gallagher; the summary for these studies is:

PMR $643/630 = 1.02$ (95% CI 0.94-1.10)

With the exception of the study of Bates that indicated a non significant excess risk associated with employment duration, all of the other studies (Demers 1994, Aronson, Baris, Beaumont, Guidotti) showed no evidence of increased risk with employment duration.

Conclusion: All study designs (incidence, mortality and PMR) are consistent in documenting no increased risk of lung cancer.

- This reviewer concurs with the interpretation of the authors of the CCO report that there is no evidence of an increased risk of lung cancer associated with the occupation of firefighting.

4.7 Multiple myeloma: The summary of the studies reviewed by CCO as described in the first two paragraphs are accurate. The total number of observed cases and expected controls and this reviewer's summary risk measures for 2 incidence studies reported in Figure 7 (page 26) and 95% CI is:

Incidence $7/7.8 = 0.89$ (95% CI 0.36-1.90)

The only mortality study (Baris) providing data on multiple myeloma showed a non significant excess (SMR of 1.68, based on 10 observed cases and 5.95 expected, 95% CI 0.90-3.11, attributable risk 40%).

In addition 3 studies reporting on leukemia in firefighters have been excluded by CCO: the 3 PMR studies of Burnett and Gallagher; the summary for these studies is:

PMR $38/27.28 = 1.39$ (95% CI 0.99-1.91)

One of these studies (Burnett) showed a significant excess based on 34 deaths with 22.97 expected, PMR 1.48 (95% CI 1.02-2.07).

- Overall, these results are insufficient to determine whether multiple myeloma is a risk associated with the occupation of firefighting.

4.8 Non-Hodgkin's lymphoma: The summary of the studies reviewed by CCO reported in Figure 8 (page 26) does not consider the study of Aronson that includes 3 cases of lymphosarcoma. The total number of observed cases and expected controls and the reviewer's summary risk measures for the 2 incidence and 2 mortality studies (including Aronson) and 95% CI are:

Incidence $5/3.56 = 1.40$ (95% CI 0.46-3.28)

Mortality $23/15.65 = 1.47$ (95% CI 0.93-2.21)

In addition 3 studies reporting on leukemia in firefighters have been excluded by CCO: the 3 PMR studies of Burnett and Gallagher; the summary for these studies is:

PMR $79/57.66 = 1.37$ (95% CI 1.08-1.71)

One of these studies (Burnett) showed a significant excess based on 66 deaths with 50 expected, PMR 1.32 (95% CI 1.02-1.67).

Conclusion: Excess risk is around 40%, consistent between the incidence, mortality and PMR studies, with attributable risks of 27% to 32%.

- Overall, these results are insufficient to determine whether non-Hodgkin's lymphoma is a risk associated with the occupation of firefighting.

4.8 Testicular cancer: The summary of the studies reviewed by CCO as described in the first two paragraphs are accurate. The total number of observed cases and expected controls and reviewer's summary risk measures for 2 incidence studies (this reviewer excluded the study of Stang) reported in Figure 9 (page 29) and 95% CI is:

Incidence $13/8.84 = 1.47$ (95% CI 0.82-2.64)

The only mortality study (Aronson) providing data on testicular cancer showed a non significant excess (SMR of 2.52, based on only 3 observed cases with 1.19 expected, 95% CI 0.52-7.37). None of the 3 PMR studies provided data on testicular cancer.

- Overall, these results are insufficient to determine whether testicular cancer is a risk associated with the occupation of firefighting.

Correspondence between the conclusions of the authors of the CCO report and those of reviewer PB are shown in Table 2 below.

Table 2. Correspondence between the conclusions of the authors of the CCO report with those of reviewer PB regarding risk by cancer sites.

CANCER SITE	CCO	PB
Bladder	Insufficient evidence	Insufficient evidence
Brain and CNS	Limited evidence	Probable risk
Colorectal	Limited evidence	Insufficient evidence
Colon	No conclusion	Insufficient evidence
Rectum	No conclusion	Possible risk
Kidney	No evidence	Insufficient evidence
Leukemia	Insufficient evidence	Insufficient evidence
Lung	No evidence	No evidence
Multiple Myeloma	Insufficient evidence	Insufficient evidence
Non-Hodgkin's lymph.	Insufficient evidence	Insufficient evidence
Testicular	Insufficient evidence	Insufficient evidence

B. Assessment of CCO Conclusions by Reviewer (DP)

The evaluation of consistency ought to take place in the context of at least two elements: (1) biologic plausibility; and (2) consistency between exposure and the disease(s) of interest. The summary discussions at the end of each section are non-specific and do not provide guidance to the reader on possible biologic links that may exist. The broad discussion of the epidemiology of different malignancies assists the reader in gaining an understanding of causality. However, the absence of more concise discussions limits the conclusions that may be drawn.

4.1 Bladder Cancer

Bladder cancer is one of the malignancies where the conclusion of insufficient data is troubling. It appears that most of the data point to a small and consistent increase in bladder cancer among firefighters. The authors note these increases are not statistically significant. However, they appear to be reasonably well founded based on several criteria: (1) consistency; (2) exposure; and (3) biologic plausibility. The discussion of occupational risk factors for bladder cancer is brief given the large number of studies that have been conducted concerning this problem. The discussion should be expanded to include a more significant discussion of the occupational epidemiology of this disease. These factors argue in favor of stronger conclusions than those made by the authors.

4.2 Brain and Central Nervous System Cancers

The authors note there is limited evidence to conclude there is a relationship between firefighting and central nervous system malignancies. They aptly point to the poor understanding of the relationship between central nervous system malignancies and exposure. However, as presented it appears that the limitations of available data are clearly enough discussed to present a fair representation of firefighter risk. Several conclusions may be equally valid: (1) Given the relatively rare nature of the disease(s) in question it is surprising to find the strength of the relationships seen; (2) The failure to consider confounding exposures is understandable given our poor understanding of the epidemiology of central nervous system malignancies. These factors argue in favor of stronger conclusions than those made by the authors.

4.3 Colon and Rectal Cancers

The report aptly notes, “Given that studies have reported a high chance for misclassification, colon and rectal cancers are often considered in combination. This is true for cause of death listed on death certificates where studies have documented over reporting of colon cancer and underreporting of rectal cancer (Percy et al., 1981; Reynolds et al., 1991).”

The authors conclude, “The main limitations of these studies include limited data with which to assess a dose-response relationship, limited or no data available on confounders, and limited exposure indices.” And, “These studies taken together provide limited evidence of an increased risk of colorectal cancer associated with the occupation of firefighting.” This conclusion is somewhat vague. Although many of the issues related to exposure assessment discussed earlier apply to the presentation of data on colon and rectal cancer, the conclusions appear to be reasonable based on available evidence.

4.4 Kidney Cancer: The authors state, “Three of the four incidence studies were based on fewer than five cases. The remaining study, a case control study, did not report the number of kidney cancer cases on which the analysis was based. Eliminating these studies would have resulted in insufficient data to generate a summary estimate. Eliminating five mortality studies (Beaumont et al., 1991; Aronson et al, 1994; Demers et al., 1992; Tornling et al., 1994; Vena & Fiedler, 1987) which are based on fewer than five kidney cancer cases would leave only two mortality studies. A summary risk estimate was not recalculated.”

The elimination of so many studies has limited justification. Indeed such a limitation in the case of a relatively rare disease impairs the ability to detect disease. A summary estimate should be computed for kidney cancer inclusive of these studies. The authors conclude, “These studies taken together provide no evidence of an increased risk of kidney cancer associated with the occupation of firefighting.” The work of Burnett (1994) should be included in the summary estimates even if it is a PMR

4.5 Leukemia: Leukemia and lymphomas are often aggregated in disease studies. While it is outside the scope of this review to critique the problems associated with these methods (i.e., disease aggregation) the review conducted is not clear on how this issue was managed.

In a study conducted by Guidotti, T., results suggest that firefighters are at an increased risk of leukemia (SMR = 126.5; 95% CI: 60.6-232.5). Although the data were not statistically significant, suggestive excess was observed. Based on a proportionate mortality study by Feuer, E., et al., it was found that white firefighters were at an elevated risk of almost 3x's (PMR: 2.76) that of white police to develop leukemia (p<0.05).

The authors conclude, “These studies taken together provide insufficient data to determine whether or not there is an increased risk of leukemia associated with the occupation of firefighting.” Inclusive of data from proportional mortality studies the evidence appears to tilt in favor of concluding there is a relationship between firefighting and leukemia. This is supported by the authors' statements concerning exposure which read, “Leukemia has been associated with exposure to benzene, formaldehyde, styrene, 1-3 butadiene, and vinyl chloride. Firefighters have the opportunity for exposure to all these agents. Studies have reported concentrations of benzene and formaldehyde at structural fires which exceed NIOSH or ACGIH ceiling or short-term exposure levels.” It is not clear how (or if) the authors account for exposure data in drawing their final conclusions

4.6 Lung Cancer: The review of lung cancer mortality should include more discussion on the possible impact of cigarette smoking. Analysis of available work should include estimates of mortality from smoking-related non-cancer (e.g., emphysema) and determinations made about the possible impact of smoking. Once this determination is made the authors should

address the following question: Is it possible that non-smoking fire fighters are at increased risk of lung cancer. The discussion concerning how smoking may have impacted lung cancer mortality is of great importance. For example, lung cancer mortality ought to be evaluated in the context of mortality from other smoking-related causes (e.g., other respiratory illness). Data argue in favor of stronger conclusions than those made by CCO. Increased attention should be given to possible exposure to respiratory carcinogens.

4.7 Multiple Myeloma: The authors conclude, “These studies taken together provide insufficient data to determine whether or not there is an increased risk of multiple myeloma associated with the occupation of firefighting.” Although there is considerable variability in the risk relationship between fire fighting and risk of multiple myeloma, the data presented below support the contention that there is a relationship between fire fighting and multiple myeloma. The authors need to include more discussion on environmental causes of multiple myeloma.

The authors write, “Two studies (Demers et al., 1993; Baris et al., 2001) report analyses by duration of employment. These data may be found in Table 22. There is a suggestion of increased risk with increasing years of employment although the numbers in both studies are small. Baris and colleagues report a significant mortality risk increase of 2.31 (95%CI: 1.04, 5.16) for those employed 20 years or more. Demers and colleagues report an elevated risk of 2.90 (95%CI: 0.4, 21.6) among those employed 10 years or more although this was not significant.”

4.8 *Non-Hodgkin Lymphoma*: The authors conclude, “These studies taken together provide insufficient data to determine whether or not there is an increased risk of non-Hodgkin lymphoma associated with the occupation of firefighting.” As with other malignancies, statistical data should be weighted with data on exposure and occupational causes of morbidity.

4.9 *Testicular Cancer*: The authors conclude, “These studies taken together provide insufficient data to determine whether or not there is an increased risk of testicular cancer associated with the occupation of firefighting. These four studies report an increased risk among firefighters; however, additional studies are required.”

Evidence presented by the authors appear to conflict with this conclusion. The authors state, “The risk estimates reported by three incidence studies range in magnitude from 1.15 to 4.30, with the highest estimate being reported by a case control study. Two of the three studies were based on fewer than five cases (Stang et al., 2003; Giles et al., 1993). The estimate of the mortality study, at 2.52, falls within the range of these studies.” The small number of cases reflects the relative rarity of the disease.

5.0 Discussion

In considering the review criteria defined by Bradford Hill, careful consideration needs to be given to the consistency of association in addition to the strength of association. The evaluation of consistency ought to take place in the context of several elements: (1) biologic plausibility; and (2) consistency between known and/or hypothesized exposure(s) and the disease(s) of interest. This can only happen with a broad discussion of the relationship between each exposure and cancer. This needs to be done for each type of malignancy. The final report begins this process but does not go far enough. For example, has the described association been repeatedly observed in more than one group, in different places, and under different circumstances? With regard to biologic plausibility there is little discussion to help the reader clearly understand the nature (i.e., magnitude and extent) of exposure and how this might be mitigated through the use of protective equipment.

The authors provide a great deal of weight to the strength of statistical association; however, it appears they largely ignore other Bradford-Hill criteria in their final conclusions. There is

no inherent reason that statistical significance should be weighted more heavily than other Bradford-Hill criteria. In other words, the authors attribute causality on what is largely a statistical number and not the sum of the relationships between the different elements that the Bradford Hill uses to determine causality. This substantively impairs the ability of the reader to render reasonable conclusions based on a summary of all evidence including exposure and the relationship between exposure and disease.

With regard to the question of exposure there are some conflicting comments within the document provided. For example, the authors cite the work of Siemiatycki (1991) and note the challenge of long-term exposure assessment among occupational cohorts (see background, section 1). However, the reviewers also point to the limitations of “individual exposures or exposure indices.” This appears to be used as a justification to limit the scope of conclusions towards the null (i.e., no relationship between firefighting and work); however, the opposite conclusion may also be legitimately drawn.

The criteria as interpreted in the report presented to the Workers’ Compensation Board of British Columbia apply strict statistical criteria to issues of causality. While some studies show little or no increased cancer risk, others show credible evidence of excess risk. All aspects of evidence need to be weighed against the size of the population under study. In particular, is there credible evidence of a relationship between disease and exposure? The link between exposure and disease is not well defined within the report. The authors summarize much of their data in Table 27. For four malignancies they state that data are insufficient, limited evidence in one case and no evidence to support a relationship in two instances.

In several areas of the report the authors state that further study is required in order to reach a conclusion concerning causality. This is no doubt true but does not assist the Workers’ Compensation Board nor does it provide substantive input to the provincial fire departments. Best evidence must be weighed in the absence of additional studies. Such studies are (1) expensive; (2) time consuming; and (3) not likely to be completed within a reasonable time period.

NIOSH data bases ought to be searched as well as the data bases within the National Library of Medicine. A search conducted of the NIOSH data bases found over 200 documents that might be relevant to the questions posed by the Workers’ Compensation Board. Although many of these documents are related to the investigation of fatal injuries, others provide comprehensive summaries of exposures to fire firefighters (e.g., see NIOSH Publication No. 2004-115: Issues Related to Occupational Exposure to Fire Fighters, 1990 to 2001)

Appendix A

Reasons for exclusion should be specified in a distinct entry under each excluded study.

Appendix B

The Title “The Occupation of firefighting: Assessment of the Literature” is misleading. The authors summarize each study without providing an evaluation and a conclusion, they are not assessing the literature. The order in which cancer sites appear is not consistent with the order in the text. The authors should have analyzed and provided conclusions on all cancer sites that appear in the appendix.

References:

Lamm SH, Walter AS, Wilson R, Byrd DM, Grunwald H. Consistencies and inconsistencies underlying the quantitative assessment of leukemia risk from benzene exposure. *Environ Health Perspec* 1989;82:289-297.

Centers for Disease Control and Prevention. A Summary of Health Hazard Evaluations: Issue Related to Occupational Exposure to Fire Fighters, 1990-2001. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, January 2004. Publication No. 2004-115.

Silver SR, Rinsky RA, Cooper SP, Hornung RW, Lai D. Effect of follow-up on risk estimates: A longitudinal examination of the relative risks of leukemia and multiple myeloma in rubber hydrochloride workers. *American Journal of Industrial Medicine* 2002;42:481-489.

1. Rhomberg L, Kang JH. Breast cancer risk factors: what do we know and how well we know it. *Harvard Center for risk Analysis. Risk in Perspective* 1998; 6:1-4