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Mr. Joel Carr, National Representative
UNIFOR
205 Placer Court
Toronto, ON M2H 3H9

Re: Review, GE Peterborough Study

Dear Mr. Carr:

Thank you for asking me to review this study. I have no conflict of interest in providing this review.

By way of qualifications, I am a board-certified occupational medicine physician and internist and an epidemiologist. I am Professor and Director of the Barry Commoner Center for Health and the Environment at Queens College, City University of New York and an Adjunct Professor of Preventive Medicine at Mount Sinai School of Medicine. I received my BA from Yale University, MD and doctorate in epidemiology from Columbia University, and completed residencies in internal medicine at Montefiore Hospital and in occupational medicine at Mt. Sinai School of Medicine. My areas of research interest are occupational cancer; asbestos-related diseases; immigrant occupational health; and surveillance of occupational injuries and illnesses, publishing 99 journal articles and book chapters. I am Editor-in-Chief, *American Journal of Industrial Medicine* and Associate Editor of a major textbook, *Environmental and Occupational Medicine (4th edition)* (2007). I currently serve on the Board of Scientific Counselors of the U.S. National Toxicology Program and on the U.S. NIOSH Scientific and Technical Advisory Board of the World Trade Center Health Program. I also chair the Advisory Board on Toxic Substances and Worker Health of the U.S. Department of Labor. Finally I direct the largest occupational medical screening program in the U.S., having provided over 48,000 examinations to more than 30,000 DOE workers from 1998 to the present, including the use of low dose CT scanning to screen over 13,000 workers for the purpose of early lung cancer detection. I attach my C.V.

I reviewed the report entitled "Peterborough Health Study, GE Canada, Final Report (Update II: February 2003) ("Report"). I praise the authors for the hard work that the report represents, the diligence in explaining study methods and results in accessible language, and the

fact that the overall effort represented a serious effort to respond to concerns raised by workers or former workers at the plant.

General Comments

1. Scientific health studies that are undertaken to address important questions normally undergo peer review, either in the process of journal publication or as part of the study itself. Peer review is an important element of study quality. I see no reference to peer review in the Report except for some brief comments by Dr. T. Haines. I checked the very comprehensive database of medical literature, PubMed, and saw no evidence that the study has been published. It does not appear to have undergone full peer review.

2. The provenance of the study was not described. Was the study funded by GE? More importantly, did the authors work either directly or under contract for GE? (The answers to these questions are in your cover letter but not in the report.) These questions are not only important as routine and customary elements of disclosure. They pertain to the question about whether the company (or union) had any decision-making about the design, conduct, analysis, and reporting of the study. Decisions about these study elements must be under the control of the study investigators and should be explicitly addressed in the report. This issue was not addressed in the Report or in your cover letter.

3. Epidemiologic method The study uses a proportionate mortality approach. It is not the preferred method in occupational epidemiology due to inherent limitations (1-2). The Report authors cite some of these limitations (p. 7). An uncited limitation is that the proportions of the causes of death of interest may be distorted if the study exposures or some attribute of the exposed group affects the proportions of the other causes of death. The authors do not specify why they chose this study method, which is usually selected, because it is relatively inexpensive, can be done quickly, and/or the entire cohort cannot be identified. A second problem (p. 7) is that we do not know whether the deaths included in the study are representative of all deaths among exposed workers. If they are not, then the resultant analysis may yield biased and inaccurate results. I saw no discussion of the likelihood that these limitations were important in this particular study and how they might limit conclusions.

4. Plant exposure characterization The method of assigning exposures to plant workers is a critical part of the study, and considerable effort was made to complete this task and describe it in the report. Frankly, though, I am not confident that it was grounded in reality for several reasons.

    a. First, the authors provide NO data on environmental sampling/industrial hygiene measurements, despite the fact the plant operated for 6+ decades by the time the study was done. If data were available and used, they should have been included in the report. If such data exist, it is unlikely that they amply represent exposures

throughout the plant for the simple reason that industry in general did not perform, and had no reason to perform, such representative testing.

b. The authors used the TWA's extant in 2000 to grade exposures. Since TWA's from previous years (Phase II, Appendix 10) were much higher, it isn't clear why 2000 TWA's were used. My hunch is that historical exposures were recorded or considered to be low by the authors (and plant employees), but it isn't explained. Regardless of the reason, few workers appeared to have high exposure, at least to asbestos, according to the classification of the authors.

c. The authors judge the impact of plant controls (ventilation, respirator use) in limiting exposures over the previous decades. It must be admitted that they could only crudely estimate this, even if based on interviews of plant workers. They cite no objective data. We have no idea of how well ventilation functioned decades ago and whether respirators were appropriate and used. The authors used reports of workers and plant management decades after the exposures occurred, but it is unlikely that such reports were based on testing of ventilation function or even informal surveys of respirator use. If the Peterborough GE plant was like most plants in the era when the exposures of interest occurred, it is likely that methods of control had quite limited success in mitigating exposures.

d. The authors state on p. 58 that the "major processes involving the eight carcinogens didn't change over time." The time period isn't specified, but given a study of deaths that occurred beginning in 1970, the critical exposure period would begin in 1940 and extend until about 1980. It is challenging, though possible, to believe that there were no changes in major plant processes over that 40 year period.

5. Study Group It isn't clear stated whether the entire cohort from the index plant was enumerated. It doesn't appear to be so, since the 3 lists used in the study have a total of 2,428 names, and your cover letter cited that thousands of workers were employed at the plant at some time in the past. The study group is 1970-1986 deaths of people with $\geq$ 10 years at the plant and who received pension and post-1986 deaths of people with $<$ 2 years at the plant who also received pension. The authors do not address the likelihood that they are missing deaths that might be related to exposure in a manner that would distort study results. The two separate groups that constitute the study group is also problematic scientifically, because it combines two separate groups: older workers with earlier presumably higher exposures (pre-1986) with younger workers with more recent exposures (> 1986). This conflates duration and likely intensity of exposure, making an analysis of risk by duration biased.

6. Smoking The Phase II study examines the relation between age, asbestos exposure, smoking, and lung cancer. Smoking data were obtained from medical records. There are two serious problems with this method. One-fourth of cases lacked smoking information. More importantly, medical records are highly variable in the consistency of reports on smoking, as cigarette quitters are sometimes identified as non-smokers. Finally, the analysis treats smoking crudely in that it combines all smokers, including current and former smokers. If asbestos-exposed workers quit smoking more frequently than the control group, the risk associated with asbestos would be under-estimated.

Responses to Questions Posed

Phase I

1. The PCMR method has inherent limitations. Please see my comments above (#3)

2. By definition, a mortality study does not study people, exposed or not, who have not died. It is not a good method for studying diseases that have a high survival rate. This would include certain cancers, such as bladder cancer.

3. Aggregating pre-1986 deaths of people with $\geq$ 10 years at the plant with post-1986 deaths of people with $\leq$ 2 years at the plant was an artefact of legislation and change in pension rights. It is problematic scientifically, because it combines two separate groups: older workers with earlier presumably higher exposures (pre-1986) with younger workers with more recent exposures (> 1986). This conflates duration and likely intensity of exposure, making an analysis of risk by duration biased. It also dilutes out higher exposed workers with lower exposed workers when the group is analyzed as a whole.

4. The expected number of cancer deaths can be obtained by summing the column containing the expected numbers by cancer type. The more important problem is that the authors don't provide PCMR's for causes of death other than cancer, so we can't tell whether heart disease, lung disease, etc. deaths are increased or decreased, which could affect how we interpret the cancer death results.

5. Adding Table 5,7,9, and 10 deaths would be double-counting deaths, since the groups overlap among the tables.

Phase II

1. It is possible that diesel exhaust and secondhand smoke could have influenced the results, depending on how distribution of exposure to these 2 mixtures was distributed. It would be difficult to predict.

2. Silica exposure could also have affected the study results.

3. I strongly disagree with using non-lung cancer controls. Phase I of the study showed a borderline statistically increased PCMR for the second most common group of cancers, digestive cancers among males, which account for 29% of all cancer deaths (Table 4).

4. This suggest that digestive cancers might be related to plant exposures, using them as controls would falsely diminish the PCMR for lung cancer. I understand that the use of other (non-lung) cancers as controls was done for practical reasons, but it compromised study validity.

5. See answer to previous question. It was appropriate to use dead controls, if that is a question.

6. The 1:1 case:control ratio of 1 limits statistical power, but the authors had no choice. The bigger question is whether they had enough power to answer reasonable study questions. The authors nicely provide a table on power on p. 78. The table is incomplete, though, because they don't give the prevalences of exposure on which they based their calculations.

   The Table on p. 78 appears to show acceptable power ($\geq$ 80%) for detecting a twofold increase in lung cancer risk due to asbestos. A twofold increase in risk is fairly high, especially for a group of manufacturing workers with heterogeneous exposures. This study could not rule out a 50% or 80% increase in lung cancer risk due to asbestos, for example. That is a limitation. The power for the other lung carcinogens was even worse.

   Looking at the power in relation to asbestos more closely, few workers were deemed to have "high" exposure to asbestos (8/195 among controls, or 4%) or even "high" or "medium" exposure (combined) to asbestos (31/195 among controls, or 16%). This means that the study could only detect an increase in risk of 2.5- or 3-fold associated with asbestos exposure with adequate power.

7. The Table 5 lung cancer odds ratio should be 1.9. That is less of a smoking effect than I would expect to find. However, it depends on the distribution of pack-years, smoke quit rates, and time since quitting. Also 23% and 28% of cases and controls did not have smoking information; this is a high rate of missing data.

8. The Table in your letter with multiple exposures should have 66 smoking cases. The odds ratio for smoking with "no multiple exposures" (i.e., no asbestos exposure) is 4.7. This is the estimate of the effect of smoking on lung cancer among those not exposed to asbestos. The odds ratio for smoking with "any multiple exposures" (i.e., any level of asbestos exposure) is 9.6. This is the estimate of the effect of smoking on lung cancer

among those exposed to asbestos. Thus, exposure to asbestos doubled the risk of lung cancer among smokers (from 4.7 to 9.6). I didn't calculate confidence intervals, but they are likely different ratios. This results suggest that asbestos exposure added substantially to the lung cancer risk observed among smokers.

Study Conclusions

The conclusions on p. 78 are overly broad and sparsely supported by the results and analysis. Phase I was not carcinogen-specific, and Phase II evaluated asbestos only, so conclusions that appear to address any carcinogens other than asbestos are unwarranted. The methodologic problems and the overall comments cited above make the authors' unqualified endorsement of the conclusions on p. 78 difficult to justify. The authors' statement that industrial hygiene data show that exposures were below contemporaneous TWA's is not supported by any data presented in the report. The confidence in the effectiveness of ventilation and widespread use of personal protective equipment during the relevant decades of exposure, 1940-1970 is not supported by data and at odds with my long experience in occupational medicine.

It is important to note that any epidemiological study of an entire plant that may not show an association between plant exposures and risk of specific disease does not rule out that individual plant workers has significant exposures that caused or contributed to their illnesses. If, for example, only a limited number of workers had significant exposure to asbestos, sufficiently so to raise their lung cancer risk, their excess risk may be diluted by a larger number of workers who did not have such exposure, leading to an overall risk that is not in excess. This problem is intensified, if the asbestos (and smoking) exposure are inadequately characterized. In addition, if the number of workers had significant exposure to asbestos is limited, the study is likely to have insufficient power to reliably detect an excess risk in this small group.

Final Comments

The overall GE Peterborough study is of mediocre quality. The Phase I PCMR results of elevated risks for lung cancer (including among women), Hodgkin's lymphoma (men only), digestive cancers (men only) and skin cancers (woman only) are credible, though confidence is limited by the proportionate mortality study method, the absent reporting of non-cancer deaths, the questionable representativeness of the deaths included in the study, and an unusual set of two eligibility criteria that depended on calendar year-specific pension criteria. It is unusual to see increased lung cancer in women and increased digestive cancers (in men only) in the occupational setting; this requires follow-up as there may be an occupational relation. Increased male lung cancer and Hodgkin's lymphoma are more commonly found and are plausibly related to exposure to occupational carcinogens.

The Phase II study was too poorly conducted to instill any faith in its results. The main problems were unsupported assumptions about exposure (e.g, exposure misclassification),

limited statistical power even in relation to asbestos exposure, an inappropriate use of non-lung cancer controls, and incomplete and questionable quality of smoking data. Some of these factors were beyond the control of the investigators, though the discussion of these limitations, which is a conventional element of scientific reports, was missing.

Please let me know if you have any questions.

Sincerely,

Steven Markowitz, M.D., DrPH

References (excerpts enclosed)

1. Checkoway H, Pearce N, Kriebel D. Research Methods in Occupational Epidemiology, 2nd edition. Oxford Press, 2004, 372 pp.
2. Rothman KJ, Greenland S. Modern Epidemiology, 2nd Edition. Lippincott-Raven, 1998, 737 pp.

Additional miscellaneous comments

1. Deaths that occurred out of Ontario were excluded or handled in an undescribed manner.
2. There was no description of the plant population over time.
3. Some numbers in the text are wrong. For example, p. 20 states that mean age at cancer death was 69.1 years but Table 3 says that the mean age was 68.8 years. Other similar errors occur. This is sloppy and undermines confidence.
4. Note that 44% of salaried employees used to be hourly employees (Table 2, page 30), obscuring a clear cut distinction between the two groups, and any accompanying risk. This means that the manufacturing (hourly and salaried) versus non-manufacturing is more important than the hourly versus salaried comparisons.
5. Increase in female lung cancer in occupational studies is very unusual. Note the 1970-1998 study timeframe was before lung cancer peaked in women.
6. Authors fail to comment on borderline significant results, e.g., digestive cancers and female skin cancers (Table 11). See Table 15. This reflects a poor understanding of statistics or an intention to understate the importance of the results.
7. Discussion is erroneous. p. 22 says that Hodgkin's disease was not in excess in manufacturing groups. Table 7 says clearly otherwise for manufacturing males.
8. Phase 2 should have also addressed Hodgkin's disease and digestive cancers. This was a missed opportunity.

9. Authors state on p. 4 that Phase II is a nested case control study. It is not, as the cohort from which cases and controls were drawn was never defined. The PCMR study was based a number of deaths that represents an unknown sample from an unspecified cohort.
10. P. 46, first paragraph misstates cohort definition
11. Section 3.1.5 Matching criteria for controls: 10 years for age and 11 years for hire date is quite broad.