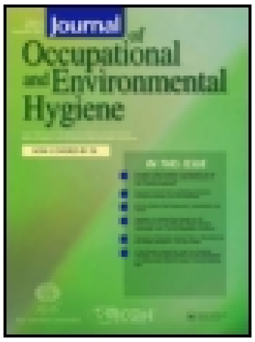

ISSN: 1545-9624 (Print) 1545-9632 (Online) Journal homepage: www.tandfonline.com/journals/uoeh20

Letters to the Editor

I. Burstyn & H. Kromhout

To cite this article: I. Burstyn & H. Kromhout (2008) Letters to the Editor, , 5:7, D73-D76, DOI: 10.1080/15459620802111525

To link to this article: https://doi.org/10.1080/15459620802111525

Journal of Occupational and Environmental Hygiene, 5: D73–D76
ISSN: 1545-9624 print / 1545-9632 online

DOI: 10.1080/15459620802111525

Letters to the Editor

STILL NO EVIDENCE THAT COAL TAR EXPOSURE CONFOUNDED THE ASSOCIATION BETWEEN BITUMEN/ASPHALT FUME AND LUNG CANCER IN THE COHORT OF EUROPEAN ASPHALT WORKERS

We read with great interest the report by Fayerweather[1] on adjustment of the results of studies carried out in the asphalt industry for co-exposure to coal tar. The validity of Fayerweather's approach to adjustment for confounding depends of course on the choice of model of confounding (borrowed from previous investigators and well accepted as a crude, yet sometimes useful methodology),[2,3] but principally on the validity of three assumptions about *intensity* and *duration* of exposure to polycyclic aromatic hydrocarbons (with benzo(a)pyrene as their proxy) due to coal tar use and *prevalence* of coal tar use in the study population. We will demonstrate that when peer reviewed published data is used to make assumptions about exposure to benzo(a)pyrene due to coal tar in asphalt mixes, especially those that are derived for the purpose of the study of the European asphalt workers coordinated by the International Agency for Research on Cancer (IARC), Fayerweather's calculations fail to support his conclusions.

Appropriate estimates of exposure *intensity* could have been easily derived by Fayerweather as illustrated below. Burstyn et al.,[4] in developing a job-exposure matrix for the study of European asphalt workers, calculated average exposure to benzo(a)pyrene in countries and time periods where coal tar use was prevalent in the industry to be on the order of 400 ng/m^3.

This estimate takes into account the diversity of paving methods and work durations (obtained in structured interviews of participating companies and reviewed in collaboration with local industry experts) and all relevant exposure measurements and validated exposure models derived from them. This estimate is an order of magnitude lower than Fayerweather's guess of exposure to benzo(a)pyrene paving with coal tar-containing asphalt: 10,000 ng/m^3 (p. 179),[1] which exceed even the maximum reported exposure in the European Union in the studied countries during the relevant time period of 8000 ng/m^3 that was measured during indoor application of mastic *tar-free* asphalt.[5] The only estimate of benzo(a)pyrene exposure associated with coal tar paving presented by Fayerweather (75 μg/m^3, in Table I)[1] comes from a secondary citation in the IARC monograph[6] of Bridbord et al.,[7] a monograph published in the United States in 1976 that reported ambient (not personal!) air concentrations near sources of emissions, results that are not likely to be representative of personal occupational exposures in the IARC cohort. Clearly, examination of available evidence does not support this key assumption of Fayerweather.

The second key estimate required to determine cumulative exposure used by Fayerweather is about typical exposure *duration* to paving with coal tar-containing materials. Examination of published results[8] clearly indicates that mean duration of employment of the cohort members in the asphalt industry was much less than 20 years and that duration of exposure to "coal tar" would likewise be even shorter. Furthermore, according to Table 6.1.1 of the IARC internal report[9] ("Mortality by Duration of Exposure to Tar (years) All Countries, Only Subjects with More than One Season of Employment") the duration of exposure to coal was categorized (in years) into "non-exposed," "<1.4606," "1.4606–<3.0869," "3.0869–<7.1047," and ">7.1047" with the associated person-years: 861,102, 94,933, 66,705, 84,124, and 88,747, respectively. Consequently, only 7% of total person-years and only 27% of person years with exposure to coal tar are in the "7 years" category, which suggests typical duration of exposure to tar that is much less than 20 years.

Lastly, the correct estimate of duration of exposure to coal tar should take into account the seasonal nature of paving and roofing,[4] which can be as short as a quarter of a year in Nordic countries that dominate that IARC cohort. Therefore, 20 years of *exposure* to coal tar in the asphalt industry assumed by Fayerweather translated into 80 years of employment in the asphalt industry, which is implausible. A much more reasonable yet generous guess is that a typical asphalt worker in the IARC cohort worked no more than 10 years with coal tar-containing mixes. It must be noted that in the companies enrolled in the IARC cohort, coal tar use was discontinued during the follow-up, as early as in 1960s and 1970s in many jurisdictions/companies, which makes Fayerweather's postulated 20-year duration of coal tar exposure entirely unreasonable for the relatively young cohort with recent years of entry, i.e., the cohort of European asphalt workers.

The consequence of errors made by Fayerweather in making these assumptions is a serious overestimate of possible confounding by coal tar. If we use the 400 ng/m^3 estimate of benzo(a)pyrene exposure during paving with tar-containing materials and a reasonable guess of duration of exposure to coal tar (10 years), the estimate of typical exposure to benzo(a)pyrene due to coal tar becomes 4 $\mu g/m^3$-years. Using expression (6) of Fayerweather, relative risk due to coal tar in paving is $RR_{coal.tar|paving} = UUR_{cum.exp=4} = 1.17^{4/100} = 1.0063$. This estimate is based on defensible assumptions, is much smaller than that obtained by Fayerweather: $RR_{coal.tar|paving} = 1.37$, and is not distinguishable from unity.

If $RR_{coal.tar|paving} \sim 1$, then coal tar use is unlikely to either cause lung cancer in the cohort, let alone confound any other associations. This is clearly seen from examination of Fayerweather's expressions (1) to (4).

If $RR_{coal.tar|paving} = 1$, then, according to expression (2), $RR_{paving} = p_{coal\ tar,\ paving}, + 1 - p_{coal\ tar,\ paving} = 1$, according to expression (3), $RR_{comparison} = p_{coal\ tar,\ comparison} + 1 - p_{coal\ tar,\ comparison} = 1$, and, finally, according to expression (4), $U = RR_{paving}/RR_{comparison} = 1$, which, together with expression (1) implies that $RR_{paving,\ adjusted} = RR_{paving,\ unadjusted}$.

In other words, we have demonstrated that the original unadjusted estimates were very unlikely to have been confounded, if we accept the logic of Fayerweather to be sound. *Note: We no longer have to consider the problem with Fayerweather's very crude approach to estimation of prevalence of coal tar use in the comparison group, since they cancel out in expressions (2) and (3).*

If we repeat the same calculations assuming that exposures in roofing are twice as intense as those in paving (an assumption that Fayerweather borrows from Burstyn et al.[8]), then the estimate of $RR_{coal.tar|roofing}$ becomes 1.012640. This again is not meaningfully different from unity, demonstrating that $RR_{roofing,\ adjusted} \sim RR_{roofing,\ unadjusted}$: no confounding by coal tar in studies of roofers. Even if we let duration of exposure to coal tar for roofers to be 20 years, then $RR_{coal.tar|roofing}$ becomes 1.03. Further, if we assume that roofers' exposure to benzo(a)pyrene was four times more intense than that of workers in paving (with 20 years of exposure), we obtain $RR_{coal.tar|roofing}$ that is 1.05. Thus, our conclusion about negligible expected confounding still holds if we make rather extreme, yet perhaps realistic assumptions on exposure to coal tar in the "highly exposed" strata of the IARC asphalt cohort.

The conclusion that one may arrive at after this *external* adjustment for confounding is that lack of confounding of the effects of bitumen/asphalt fume in the cohort of asphalt workers is due to negligible risk in the industry due to coal tar use (in the past). If true, this is reassuring and further diminishes our doubt about the extent of confounding of positive results published by Boffetta et al.[10] However, such a conclusion is equally dubious, as it implies that it was not necessary to ban coal tar use in asphalt. Surely, stronger evidence is required to draw meaningful conclusions, instead of a simplistic calculation, even if it is based on justifiable inputs. Of course, defensible adjustment for confounding due to coal tar use in the cohort (and meta-analysis of the asphalt studies) would take into account each cohort member's employment in companies that used coal tar in asphalt mixes, the type of work they actually did (e.g., hot vs. cold paving) when exposure occurred (to account for temporal trends in exposure intensity seen in this industry), and to consider the variability of coal tar content of different asphalt mixes. We allowed for all but the last matter in meticulously reconstructing exposures for the cohort members, with considerable input from (industry and union) experts on the ground.[4]

Boffetta et al.[10,11] pooled all national cohorts that are treated as eight separate studies by Fayerweather[1] and *de facto* already published a superior "meta-analysis" of the IARC cohort(s) with individual-level data, rendering much of Fayerweather's effort unnecessary. The suggestion that we most likely did not fully adjust for confounding due to coal tar use and associated exposures is most likely related to either the imprecision in reported coal tar use by the companies (phased out at different time periods across EU) or unintended exposure not recognized when coal tar contaminated layers of asphalt were being recycled. We always presented these caveats as a matter of intellectual honesty. For full discussion of this and related mater of the choice of exposure metric, the readers are advised to refer to the original papers of Boffetta et al.[10,11] and Burstyn et al.[8] instead of relying on impressions of Fayerweather.[1]

In summary, external adjustments for confounding will never achieve this level of sophistication due to crudeness of assumptions that must be made. There may be a place for external adjustments in meta-analyses in the context of sensitivity analyses but certainly not in the situations where by far the largest study on the carcinogenicity of bitumen exposure among asphalt workers with up-to-date quality of exposure assessment undertook internal correction for confounding exposures like coal tar. What does make sense is to undertake a sensitivity analysis using different assumptions about patterns of coal tar exposure in the study of European asphalt workers, results of which we recently submitted.

In the case of unmeasured confounders, it is wiser to try to collect relevant data, which is currently being done with smoking histories and personal habits of the asphalt workers in the course of an industry-funded, nested case-control study on lung cancer among members of the IARC asphalt cohort. The investigators (we among them) would be sad to learn that their effort is futile, because of superior qualities of external adjustments advocated by Fayerweather.

I . Burstyn
University of Alberta
Calgary, Alberta, Canada
H. Kromhout
Institute for Risk Assessment Sciences
Utrecht, Netherlands

REFERENCES

1. **Fayerweather, W.E.:** Meta-analysis of lung cancer in asphalt roofing and paving workers with external adjustment for confounding by coal tar. In *Proceedings of the Health Effects of Occupational Exposure to Emissions*

from Asphalt/Bitumen Symposium, June 7–8, 2006, Dresden, Germany. Vol. 4, Supplement 1, *J. Occup. Environ. Hyg*. (2007). pp. 175–200.

2. **Axelson, O., and K. Steenland:** Indirect methods of assessing the effects of tobacco use in occupational studies. *Am. J. Ind. Med. 13*:105–18 (1988).
3. **Steenland, K., and S. Greenland:** Monte Carlo sensitivity analysis and Bayesian analysis of smoking as an unmeasured confounder in a study of silica and lung cancer. *Am. J. Epidemiol. 160(4)*:384–92 (2004).
4. **Burstyn, I., P. Boffetta, T. Kauppinen, et al.:** Estimating exposures in the asphalt industry for an international epidemiological cohort study of cancer risk. *Am. J. Ind. Med. 43(1)*:3–17 (2003).
5. **Burstyn, I., H. Kromhout, T. Kauppinen, P. Heikkilä, and P. Boffetta:** Statistical modeling of the determinants of historical exposure to bitumen and polycyclic aromatic hydrocarbons among paving workers. *Ann. Occup. Hyg. 44(1)*:43–56 (2000).
6. **International Agency for Research on Cancer (IARC):** *Volume 35, Polynuclear Aromatic Compounds, Part 4, Bitumens, Coal-tars and Derived Products, Shale-oils and Soots*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon: IARC, 1985.
7. **Bridbord, K., J.F. Finklea, J.K. Wagner, J.B. Moran, and P. Caplan:** Human exposure to polynuclear aromatic hydrocarbons. In *Carcinogenesis — A Comprehensive Survey, Vol. 1, Polynuclear Aromatic Hydrocarbons, Chemistry, Metabolism and Carcinogenesis*, R.I. Freudenthal and P.W. Jones (eds.). New York: Raven Press, 1976. pp. 319–324.
8. **Burstyn, I., P. Boffetta, T. Kauppinen, et al.:** Performance of different exposure assessment approaches in a study of bitumen fume exposure and lung cancer mortality. *Am. J. Ind. Med. 43*:40–48 (2003).
9. **International Agency for Research on Cancer (IARC):** *IARC Epidemiological Study of Cancer Mortality Among European Asphalt Workers. Final Report* by P. Boffetta, I. Burstyn, T. Partanen, et al. (IARC Internal Report No. 01/003). Lyon, France: IARC, 2001.
10. **Boffetta, P., I. Burstyn, T. Partanen, et al.:** Cancer mortality among European asphalt workers: An international epidemiological study. II. Exposure to bitumen fume and other agents. *Am. J. Ind. Med. (1)*:28–39 (2003).
11. **Boffetta, P., I. Burstyn, T. Partanen, et al.:** Cancer mortality among European asphalt workers: An international epidemiological study. I. Results of the analysis based on job titles. *Am. J. Ind. Med. 43*:18–27 (2003).

AUTHOR'S REPLY

I want to thank Doctors Burstyn and Kromhout for their interest in my paper.[1] Having reflected carefully on their commentary, it appears to me that we are in agreement on a number of fundamental propositions.

First, we share a recognition of the limitations of meta-analysis. My paper[1] discusses these limitations at length (p. 193), and for those reasons I would not take issue with the commenters' characterization of meta-analysis as "a crude, yet sometimes useful methodology." Meta-analysis is an analytical tool that has been recognized by IARC [2] and many others[3–7] to be valuable in the evaluation of existing epidemiological studies. The results of any meta-analysis must be viewed cautiously, and such analyses are certainly no substitute for using sound scientific methods to develop empirical data to resolve uncertainties.

The second area of agreement follows directly from the first. Burstyn and Kromhout conclude that the analyses presented in my paper do not negate the need for the additional investigations of confounding exposures in the ongoing nested case-control study of the IARC multicountry cohort of bitumen workers. I not only agree with this, my paper (pp. 196–197)[1] presents a specific analysis that supports the decision of the IARC investigators to conduct the follow-up nested case-control study for the purposes of empirically exploring the possible role of coal tar and other confounders in the lung cancer risks observed in the study population.

Third, Burstyn and Kromhout assert that the use of external adjustments is an inferior approach to adjusting the results of the IARC Cohort Study to account for the potential confounding effects of coal tar exposures. Again, I would not say that this position is unreasonable or incorrect, and my paper certainly does not do so. It was entirely appropriate for the IARC investigators to collect empirical data on the exposures of individual members of the large multicountry cohort to bitumen and likely confounders, such as coal tar, and to specifically evaluate those data in assessing the potential for confounding in their specific study population. Indeed, I applaud the effort to undertake such a prodigious and difficult task.

My paper, however, addresses the somewhat different question of how to reconcile the IARC findings as part of a meta-analysis that includes up to forty different studies. The fact that my evaluation led me to propose that an external adjustment for confounding is the better approach for this purpose neither states nor implies any criticism of how the IARC investigators chose to design, conduct and interpret their study. Quite the contrary, my analysis (pp. 196–197)[1] specifically supports the findings of the IARC investigators with respect to their own internal adjustments. What is more, the paper (pp. 193–196)[1] includes a detailed discussion of the advantages and disadvantages of both the internal and external adjustment approaches. It also presents (pp. 195–196)[1] an alternative analysis that specifically incorporates the IARC internal adjustments for coal tar confounding. The results of the alternative analysis based on internal adjustments are highly consistent with the primary analyses based on external adjustments, irrespective of which internal exposure metric is used, except for "quantitative average" bitumen exposures that the authors discounted as biologically implausible. [8]

Burstyn and Kromhout challenge the exposure assumptions used in my paper and suggest that the internal exposure estimates they developed for the IARC cohort study should have been used instead. The commentary does not do justice to my analysis of the available scientific data on exposures, but rather than retrace those steps here, I will ask those interested to review the discussion in my paper (pp. 178–179).[1] What does merit further analysis is the commentary's observation that use of the internal IARC exposure estimates in the external adjustment analysis would have led to the conclusion that coal tar did not confound the risk findings in the IARC cohort study. As shown in the commentary, this conclusion follows directly from the fact that the internal IARC exposure intensity estimates are lower than the estimates used in my paper by a factor of 25.

Retrospective exposure reconstruction is not, of course, anywhere close to an exact science, and it is always wise to ask whether an important assumption or factual interpretation is reasonable in light of other available data. In the case of the internal IARC estimates of exposure, one way to do this is to consider whether they make sense when evaluated in light of the risk findings of the IARC study itself. In the context of the meta-analysis, this can be done by replacing the unit relative risk (URR) for coal tar used in my paper (1.17, based on Armstrong's meta-analysis of PAH-related lung cancer risks)[9] with a URR estimated specifically from the IARC study. This approach has the additional advantage, in the present setting, of adhering to the premise of Burstyn and Kromhout that internal adjustments are a superior approach for accounting for confounding.

Fortunately, this task can readily be accomplished. In developing their PAH-lung cancer meta-analysis, Armstrong et al.[9] (p. 976) derived an IARC-specific exposure-response model (URR = 44.9) from IARC's internal report (Table 8.9.4).[10] Substituting the internal IARC average PAH exposure estimate [Burstyn and Kromhout] of 400 ng/m^3 (0.4 ug/m^3) into the IARC-specific Armstrong model, and retaining all other assumptions from the meta-analysis, yields a RR due to coal tar in paving ($RR_{\text{coal tar|paving}}$) of 1.36. If PAH exposures in roofing are assumed to be twice as intense as those in paving (as is the case in the internal IARC exposure model), then the IARC-specific Armstrong model predicts a RR due to coal tar in roofing ($RR_{\text{coal tar|roofing}}$) of 1.84. Thus, coupling IARC's internal estimates of PAH exposure with the IARC-specific Armstrong model produces estimates of RR due to coal tar in paving and roofing that are not materially different from those used in the meta-analysis ($RR_{\text{coal tar|paving}} = 1.37$, $RR_{\text{coal tar|roofing}} = 1.87$).[1]

While it is reassuring to find that this analysis confirms the one presented in my paper, what is perhaps most interesting about this analysis is the fact that the IARC-specific URR of 44.9 estimated by Armstrong et al.[9] is considerably larger than the URR of 1.17 developed for studies of coke oven, gasworks, and aluminum production workers (p. 975). Because the small elevation in lung cancer risks found in the IARC cohort study cannot explain this discrepancy, misclassification of the prevalence, intensity, and/or duration of coal tar exposures is certainly a plausible explanation for the difference. The findings of the meta-analysis make it the most likely explanation. The analysis thus provides another source of support for the conclusions of the IARC investigators that the internal adjustments for coal tar in the cohort study were incomplete, and that a follow-up, nested case-control study based on individual estimates of exposure is needed to disentangle the effects of bitumen fumes and potential confounders such as coal tar.

For these reasons, I join Burstyn and Kromhout, as well as the other investigators and sponsors (my employer among them) of IARC's ongoing nested case-control study, in the hope that the study will yield the clarity that is lacking in the studies and analyses that have been done thus far. Until that time arrives, however, I find nothing in the commentary that undermines my original conclusions. Within the constraints imposed by the available data and the analytical tools available, the meta-analysis presented in my paper points to coal tar as a primary explanatory factor for the wide variation in results among asphalt worker studies with stronger methodological designs.

William E. Fayerweather
Owens Corning
Toledo, Ohio

REFERENCES

1. **Fayerweather, W.E.:** Meta-analysis of lung cancer in asphalt roofing and paving workers with external adjustment for confounding by coal tar. In *Proceedings of the Health Effects of Occupational Exposure to Emissions from Asphalt/Bitumen Symposium, June 7–8, 2006, Dresden, Germany*. Vol. 4, Supplement 1, *J. Occup. Environ. Hyg.* (2007). pp. 175–200.
2. **World Health Organization (WHO), International Agency for Research on Cancer (IARC):** IARC Monograph on the Evaluation of Carcinogenic Risks to Humans Preamble. Lyon, France: WHO, IARC, 2006.
3. **Partanen, T., and P. Boffetta:** Cancer risk in asphalt workers and roofers: review and meta-analysis of epidemiologic studies. *Am. J. Ind. Med. 26(6)*:721–740 (1994).
4. **Blair, A., J. Burg, J. Foran, et al.:** Guidelines for application of meta-analysis in environmental epidemiology. *Regulat. Toxicol. Pharmacol. 22*:189–197(1995).
5. **Greenland, S.:** Meta analysis. In *Modern Epidemiology*, 2nd edition. K. Rothman and S. Greenland (eds.). Philadelphia, Pa.: Lippincott-Raven Publishers, 1998. pp. 643–673.
6. **Petitti, D.:** *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*, Second Edition. Monographs in Epidemiology and Biostatistics, Vol 31. New York: Oxford University Press, 2000.
7. **Stroup, D.F., J.A. Berlin, S.C. Morton, et al.:** Meta-analysis of observational studies in epidemiology: A proposal for reporting. *JAMA 283(15)*:2008-2012 (April 19, 2000).
8. **Burstyn, I., P. Boffetta, T. Kauppinen, et al.:** Performance of different exposure assessment approaches in a study of bitumen fume exposure and lung cancer mortality. *Am. J. Ind. Med. 43*:40–48 (2003).
9. **Armstrong, B., E. Hutchinson, J. Unwin, and T. Fletcher:** Lung cancer risk after exposure to polycyclic aromatic hydrocarbons: A review and meta-analysis. *Environ. Health Perspect. 112(9)*:970–978 (2004).
10. **International Agency for Research on Cancer (IARC):** IARC Epidemiological Study of Cancer Mortality Among European Asphalt Workers (IARC Internal Report No 01/003) by P. Boffetta, I. Burstyn, T. Partanen, et al. Lyon, France: IARC, 2001.