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Letter to the Editor

RE: Asbestos in Brakes: Exposure and Risk of Disease

To the Editor:

Dr. Teta has claimed that my review of the issues surrounding the ability of asbestos to cause disease in persons exposed to asbestos from brakes does not meet her standards of equivocal or weight-of-evidence. Dr. Teta's comments are related only to mesothelioma, a sentinel disease for asbestos exposure [Mullan and Murthy, 1991], while my paper discusses all asbestos-related diseases.

Dr. Teta asks if "consistency in epidemiological studies that suffer from "imprecision" justify a conclusion that the evidence is "equivocal"?" As Ahlborm et al. [1990] report "It should, however, be of equal importance to evaluate those studies which do not suggest any effects of a particular exposure on the risk of disease, i.e., studies in which the effect measured is estimated to be near the null value." In my paper I have evaluated such studies and have pointed out why we cannot rely solely on them for determination of cause and the reason why the epidemiology is equivocal.

Weight-of-evidence recognizes much more than just epidemiology, as defined by the Agency for Toxic Substances and Disease Registries (ATSDR)[1], in making causal associations. I do point out the inherent limitations of human observational data and place it in context with the experimental data as well as the available exposure data. As pointed out by Dr. Sven Hernberg, Editor Emeritus of the Scandinavian Journal Work Environment and Health, "A truly negative study must (i) be large, (ii) be sensitive and (iii) have well-documented exposure data." [Hernberg, 1981].

One of the most widely acclaimed methodologies for determining cause and effect for general causation was proposed by Sir Austin Bradford Hill in 1965 [Hill, 1965]. In using this methodology, researchers are asked to evaluate nine areas of consideration: strength of association, temporality, biologic gradient, consistence, specificity, biologic plausibility, coherence, experimental evidence, and analogy. As Hill noted, "[n]one of my nine view points can bring indisputable evidence for or against the cause and effect hypothesis, and none can be required as a sine qua non." Instead, he emphasized that the responsibility for making causal judgments rested with a scientific evaluation of the totality of the data. He further acknowledged that decisions on causation must be made in the absence of perfect data. Dr. Teta has chosen to base her criticisms of my paper without a through review of other factors as suggested by Prof. Hill.

Let us look at these nine criteria individually in determining whether the data are equivocal and whether the weight of the evidence is lacking in supporting the contention of no relationship with exposure to brakes, containing asbestos, and the probability of asbestos-related disease.

First, strength of association is a reflection of the strength of effect in a given study. The epidemiological studies conducted to date have suffered from a variety of impressions and confounders, as I have pointed out, and thus cannot be used by themselves to justify a no-effect conclusion.

Second, temporality requires that the cause precede the effect. In each of the studies referenced by myself and Dr. Teta this has been true.

Third, biologic gradient is the existence of a dose-response relationship for the proposed cause-effect combination. Experimental studies and epidemiological studies of asbestos have demonstrated such a dose-response relationship. Specifically the studies of brake workers that have examined this issue have shown this dose-response effect; for example Iwatsubo et al. [1998] clearly came to this conclusion.

Fourth, consistency requires that a proposed effect be observed repeatedly under different circumstances. While some of the epidemiology studies have been consistent in

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Accepted 26 May 2004
DOI 10.1002/ajim.20061. Published online in Wiley InterScience (www.interscience.wiley.com)

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[1] Weight-of-evidence—"A weight-of-evidence analysis involves the balanced review and integration of relevant exposure, toxicologic, epidemiologic, medical, and health outcome data to help determine whether exposures to contaminant levels under site-specific conditions might result in harmful effects" [ATSDR, 2004].

their lack of significance, they have also been consistent in their lack of strength to detect an effect either due to size, confounders or lack of sufficient work histories.

Fifth, specificity requires that each cause have a single effect. This is rarely a useful criterion when dealing with environmental carcinogens because most of them cause more than one type of cancer [Monson, 1996]. Such is the case with exposure to asbestos.

Sixth, biologic plausibility seeks to determine if the theory of causation fits known mechanisms of injury causation. While it is impossible to have a complete understanding of the mechanisms of cancer causation, the biologic facts known about the various asbestos fibers are clear that they cause both non-malignant and malignant diseases in experimental systems, animals and humans.

Seventh, coherence asks if the causal theory is not inconsistent with what is already known of the injury or disease. There is no biologic argument that explains why asbestos is incapable of causing asbestosis, lung cancer or mesothelioma in one person while not in another.

Eighth, experimental evidence can consist of laboratory studies, animal studies, controlled clinical trials, or observational pathology studies. The data in my paper support such evidence.

Ninth, analogy asks if epidemiological and other studies have established that an environmental exposure analogous to the exposure being considered may cause diseases similar to those reported for the exposure being considered. Lemen [2004] clearly supports this analogy.

Dr. Teta states that "Two other negative case-control studies were not discussed, both of which examined the risk of mesothelioma in vehicle mechanics, excluding men who also worked in occupations known to pose a mesothelioma risk due to asbestos exposure [McDonald and McDonald, 1980; Agudo et al., 2000]." The McDonald and McDonald paper simply stated that "There were small excesses of some occupations but none in the larger groups—notably garage, maintenance, and transport work." This paper does not contribute to our knowledge of brake exposed workers since the paper gave no idea of whether exposures even existed to brakes in the three categories mentioned, such an assumption is pure speculation without giving detailed exposure data. Agudo et al [2000] is included in my paper and as the authors suggest the mechanics, motor vehicles category does have risk of asbestos exposure, however, the numbers were quite small, three cases from which to draw causal relationships and for this reason I included them only in my list of total cases reported.

When Dr. Teta uses PMR/PIRs less than 1.0 it is not clear to what diseases or studies she is referring. Take for example, Petersen and Milham [1980] who report an increase for the automobile and repair category (472) for lung cancer, a disease causally associated with asbestos exposure. In a later analysis of the same data base [Milham and Ossiander, 2001] report excesses in lung cancer and bronchus (ICD-7) for all age groups except ages 20–29 above 1.0 in the Automobile Mechanics and Repair Workers category [472]. They also report seven cases of mesothelioma of the pleura with six of them occurring in the age group that could potentially have the longest latency, age group 70–79 [PMR = 184].

As indicated in the Technical Notes associated with the Occupational Mortality Database of the Washington State Department of Health, from which Petersen and Milham [1980] and Milham and Ossiander [2001] data come from, PMRs are of greatest value in studies where mortality rates cannot be calculated due to a lack of information on the population at risk, particularly exposure history (www3.doh.wa.gov/OCCMORT/HTML/OMtechnotes.htm, 3/16/2004).

If Dr. Teta is referring to not including these papers into my count of mesotheliomas, then I thank her since the omitted articles add at least another 49 cases to the list of mesotheliomas reported among persons potentially exposed to asbestos from brakes [Olsen and Jensen, 1987; Coggon et al., 1995; Milham and Ossiander, 2001].

The Coggon et al. [1995] paper relies only on the occupation as listed on the death certificate, which can be misleading since a thorough examination of the decedents entire work history and their potential for exposure through home related brake work must be considered. Also, it must be kept in mind that PMR analysis is not equivalent to establishing a relative risk (RR) or an odds ratio (OR) and that they only measure relative frequency of a particular cause among all causes of death in the data set analyzed [Colton and Clapp, 2000]. While this study reports PMRs of 46 (12 deaths from pleural cancer); 88 (3 deaths from peritoneal cancer); and 80 (2 deaths from asbestosis) the authors have not given the deaths from all causes in this category of motor mechanics, as they have for the other groups they list in their job group table, making interpretation of their findings difficult. Important findings of this study, which I did not include in my paper, are the author's conclusion that when assuming a linear exposure-response that pleural mesothelioma may be underestimated.

Olsen and Jensen [1987] report on 93,810 cancer cases by occupation in Denmark for the years 1970–1979. While this study does not report specific cancers for brake repair workers the data do support an excess of mesothelioma and lung cancer in occupations that may have included brake repair workers, however, there is no way to specifically identify brake repair exposures. For example, out of a total of 426 cases of mesotheliomas, the authors found that the SPIR for transport and communications to have 27 observed mesotheliomas when only 18.1 were expected. Excesses were also found when looking at subgroups of transport and storage. Most of the subgroups experienced elevated risks of mesothelioma with 21 cases observed and 13.5 expected (SPIR 155; 95% CI: 101–238). For the category of repair of

motor vehicles and motorcycles 34 lung cancers were observed, but were not significant and no mesotheliomas were observed. The question remains, how many performed brake work versus how many did not? Further analysis needs to be done to identify specific exposures to asbestos from brakes before this study can contribute to our knowledge concerning brake repair workers and potential diseases from asbestos. While mesothelioma accounts for only 0.3% of the total cancers during this period in Denmark, the authors say a "substantial increase [of mesothelioma] in incidence has taken place since the inception of the Danish Cancer Registry in 1942."

Hodgson et al. [1997] like the other surveillance data base studies, is quite useful for evaluating overall general categories of cancer mortality trends, but not specifically useful when looking at very specific occupational categories or where the risks may be small. The authors report PMRs for 27 groups of males 16–74 and have a table of 25 job groups where the PMRs exceeded 100. Motor mechanics were not included in this list and puts them into the lower category. The authors point out that the confidence interval for motor mechanics is wide. It should be noted that "Where risks are small *P* values may well mislead: confidence intervals are likely to be wide, indicating considerable uncertainty" [Altman and Bland, 1995]. The lack of detailed occupational histories again is a problem with this study. Does this mean no risk?

Dr. Teta states that she and her colleagues obtained data from the Spirtas et al. [1985] study, using the SEER database, and after re-analysis found no associations with brake work citing a paper in press by Hessel et al. [2004]. I would caution that without detailed occupational histories many specific occupational exposures can be overlooked. Take for example the analysis by Pinto et al. [1995], where nine cases of mesothelioma, diagnosed at their Institute, which would have gone into the "idiopathic" category had not diligent interviews with the patients and their relatives, by a trained medical doctor, been conducted. Does the Hessel et al. [2004] study meet such through an examination? Without being able to examine a paper "in press" or "Letter to MJ Teta from JT Walker" of NIOSH, an answer to this question is impossible and leaves me unable to make further comment [Walker, 2002].

While I agree with Dr. Teta that epidemiological studies provide the best data for causation, which she contends have been done, however, it is not adequate to rely upon them when they suffer from inadequacies. She points out. "...ignoring or misrepresenting the available evidence from epidemiological studies cannot be defended." When one looks at the true weight-of-evidence, as I have in my paper, the five million people, whom Nicholson et al. [1984], estimated to have been vehicle mechanics, in the US, at some time in their careers deserve no less than a through review of the all the evidence before determining that no causal association exists between brake exposures from asbestos. As stated by Phil Alderson, Associate Director of the UK Cochrane Centre "We need to create a culture that is comfortable with estimating and discussing uncertainty" [Alderson, 2004]. Therefore, the conclusions of my paper can not be ignored, by the serious researcher, in determining the causal association between asbestos exposures to brake workers and disease.

Richard A. Lemen, PhD, MSPH*

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