Reply to "No Increased Risk for Mesothelioma in Relation to Natural-Occurring Asbestos in Southern Nevada"

In Response:

We appreciate the interest and review of our paper[1] by Pinheiro and Jin,[2] as they provide us an opportunity to reopen a dialogue with the Department of Health and Human Services, Nevada, with whom Dr. Pinheiro is associated.

Environmental epidemiology is a relatively recent science, and because it deals with small numbers and exposures that cannot be assessed on individuals, it uses specific methods that are different from classical cancer epidemiology.[3]

Pinheiro and Jin: "the proper indicator of risk in a population or a subpopulation is the incidence rate." Although this is often true, it would be incorrect for this situation because most mesotheliomas are due to occupational exposure to asbestos,[4] and therefore, the incidence (or mortality) rates reflect the process and/or use of asbestos in the studied area. Incidence rates cannot distinguish between occupational and environmentally caused mesotheliomas. Occupational exposure leads to a mesothelioma male:female (M:F) sex ratio of 4 to 8:1, with a mean age of diagnosis of 74 years old, because of the 30 to 50 years latency between initial exposure and mesothelioma development. In places where people were only environmentally exposed to carcinogenic fibers, the M:F sex ratio is about 1:1 and the mean age of diagnosis is 50 to 60 years.[5–7] In places where both types of exposure exist, the M:F sex ratio decreases and the proportion of young (<55 years old) cases increases, compared with places with occupational exposure only. Consequently, we used the significant decrease of mesothelioma M:F sex ratio and the increase of young cases as indicators of possible environmental exposure to carcinogenic fibers.

Pinheiro and Jin: "there is no scientific consensus on the use of the sex ratio and the proportion under 55 as indicators of environmental (non-occupational) exposure to asbestos or NOA." The epidemiology of mesothelioma from mixed environmental and occupational exposures to carcinogenic fibers has never specifically been studied. However, the studies of populations exposed to carcinogenic fibers from their natural environment, without occupational exposure to asbestos, showed a mesothelioma M:F sex ratio of about 1:1 and a higher proportion of young cases.[5–7] There are no published studies contradicting or questioning the methodology we used. The first International Conference on Mesothelioma in Populations Exposed to Naturally Occurring Asbestiform Fibers sponsored by the National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), and International Association for the Study of Lung Cancer (IASLC), will be held in Honolulu, November 9–10; methodology will be one of the topics discussed. We would welcome Drs. Pinheiro and Jin.

Pinheiro and Jin: "a male to female sex ratio can be elevated just by virtue of a low number of male cases rather than an actual increased absolute number among females." Although this statement appears incorrect—M:F would be elevated by an increase in males and / or a decrease in females—we think we understand what they mean. However, a lower mesothelioma incidence/mortality in male and in old age groups simply reflects a lower occupational exposure to asbestos. In the absence of environmental exposure, a low level of occupational exposure leads to a lower mesothelioma incidence in both males and females, and in both old and young age groups, with a M:F sex ratio still around 4 to 8:1, and less than 10% of mesothelioma cases in young individuals. If there is environmental exposure in a region where a low level of occupational exposure exists, the environmental exposure causes additional mesothelioma cases in both males and females, leading to a decreased sex ratio and increased proportion of young mesothelioma cases—as observed in Southern Nevada, whereas the total incidence in male and in old age groups may still be low compared with regions with higher occupational exposure.

Pinheiro and Jin question why the study periods are different in the incidence data that we used to compare mesothelioma incidence by state and the mortality data that we analyzed by gender, age group, and county. The answer is simple: the incidence data that we used are public, available by state only, and 2006–2010 was the longest available period of time, while the Center for Disease Control (CDC) mesothelioma mortality data that we obtained to carry out our analysis by county were available for 1999–2010. In addition, we merely cited the U.S. states that presented the lowest and highest mesothelioma incidence in the US, the lowest and highest sex ratio, and the lowest and highest proportion of young adults. We did not make any statistical comparison using these numbers, which were given as examples; we did not give any *p* value comparing Nevada and any of the seven states cited in Table 2.[1]

We thank Pinheiro and Jin for highlighting the erroneous total number of mesotheliomas in Table 2.[1] Curiously, they also made a mistake: 31,408 + 133 = 31,541 instead of 31,545 as they stated.

Pinheiro and Jin: "For the immediately younger (0–49) and older age groups (0–59) the risk in Nevada is fundamentally the same as in the US," suggesting that only the 0 to 54 years old group would be different. But their own Table 1 shows higher risk in Nevada for the 0 to 59 years old group and higher risk in the 0 to 49 years old group for Southern Nevada, compared with the US. In addition, because of the small numbers, their 95% confidence intervals are large and do not allow for any significant comparison. Consequently, incidence/mortality rates clearly cannot be used to measure environmental exposures.

Pinheiro and Jin graciously comment "We praise Baumann for producing a body of literature on mesothelioma and exposure to natural-occurring asbestos

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(NOA). The recent discovery of NOA in Southern Nevada has raised our interest in the surveillance of mesothelioma in the region." So it appears we all agree that our findings identifying environmental exposure to asbestos in Southern Nevada are important and require follow-up because asbestos causes mesothelioma. Therefore, we are puzzled by the title of their letter, a title that cannot be supported by data, and that in fact contradicts published evidence that exposure to asbestos increases the risk of mesothelioma and that such exposure is occurring in Southern Nevada.[8–10] Risk is defined as the product of hazard and vulnerability (or exposure).[11] Southern Nevadans are indeed being exposed to the hazard of asbestos fibers and therefore are at increased risk for mesothelioma and other asbestos-related diseases.[1,12] For example, ambient air measured for phase I of the Boulder city bypass showed the presence of airborne asbestos fibers.[10] Moreover, some individuals may be exposed to significantly higher concentrations through recreational activities, such as off-road vehicle recreation, horseback riding, mountain bicycle riding, hiking, and other activities that are popular in the desert areas where asbestos fibers occur.[1,8–10,13]

Environmental epidemiology is about identifying areas in which environmental risk exists and work with local experts and authorities to eliminate or at least mitigate the risk. We hope that we will be allowed to further investigate the areas in Southern Nevada where exposure occurs and where there is an apparent increase of mesothelioma among young adults. We would welcome the opportunity to work together with Nevada epidemiologists and the Nevada health authorities to help identify measures to reduce environmental exposure to asbestos and to other carcinogenic fibers and the consequent risk of mesothelioma, as we have done in other parts of the US and of the world.[6,13,14]

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Afatinib for Erlotinib Refractory Brain Metastases in a Patient with *EGFR*-Mutant Non–Small-Cell Lung Cancer

Can High-Affinity TKI Substitute for High-Dose TKI?

To the Editor:

We read with great interest the recent article by Hoffknecht et al.[1] on the efficacy of afatinib for central nervous system (CNS) metastases in patients who had undergone first-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs). We also present a case with *EGFR*-mutant non–small-cell lung cancer whose erlotinib refractory brain

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