lung cancers[5] as contributing to its demise are both wrong in view of the many original epidemiologic studies on mesothelioma by Wagner, the McDonalds, Liddell, Acheson and Gardner, deKlerk, Hughes and Weill and others that support this hypothesis. Moreover, the thrust of the amphibole hypothesis, as reemphasized recently by the McDonalds[6] and Wagner,[3] among others, is mesothelioma and *not* lung cancer. To allude to data from lung fiber burden studies, rodent toxicology, and lung cancer risks as primary bases for the advancement or refutation of the amphibole hypothesis is misconstrued. On the basis of recent mechanistic data, lung fiber burden studies, and some epidemiology, we suggested in our *Science* paper that chrysotile may be less pathogenic than crocidolite in the causation of lung cancer. However, given that smoking is a more powerful factor in lung cancer than asbestos exposure, it is more difficult to define the various roles of different types of asbestos fibers.

It is unfortunate for the readers that the "critical review" by Stayner and the accompanying postion paper by Cullen fail to cite recent proceedings and conclusions of international meetings and scientific panels endorsing the amphibole hypothesis.[7–11] Of the 72 references cited in the Stayner article, only 12 were published after 1991; half of these supported the amphibole hypothesis, but were dismissed for a rehash of earlier data previously considered by us and others.[2,7–11] Surely, the detection of mesothelioma in two individuals in Zimbabwe, a country where mesothelioma rates increasing in the general population are attributed to crocidolite,[9] is not evidence that "pure" chrysotile is the cause—especially in the absence of lung fiber burden studies.

Lastly, the section on "Mechanistic Studies" by Stayner et al. incorrectly states that experimental support for the increased pathogenicity of crocidolite is primarily derived from in vitro studies. Moreover, it fails to reference dozens of recent peer-reviewed papers by our laboratory and others (Faux, Kane, Kamp, Hei, Aust, Ghio, Weitzman, Gulumian, and others), as well as the proceedings of a conference organized by a scientist from their own institution.[12] All provide support for the role of active oxygen species in crocidolite-induced mutagenicity, protooncogene expression in mesothelial cells, and lung damage. These studies also show that crocidolite, in contrast to chrysotile at identical airborne concentrations, induces protooncogene expression in lungs and sustained proliferation of mesothelial cells after inhalation of fibers by rats,[13] thus providing a mechanistic framework for the amphibole hypothesis.

In view of these and other critical omissions by Cullen and Stayner, the "take-home" message is clear: "critical reviews" and annotations should be written by scientists with up-to-date knowledge of recent papers in the literature and in the mainstream of relevant panels and scientific meetings. Contrary to the annotation by Cullen, the amphibole hypothesis of mesothelioma was *not* dead on arrival in 1990, but is still viable. □

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5. *Cullen Responds*

I am delighted to see that Drs Mossman and Gee have appropriately narrowed the focus of the amphibole hypothesis to the question of mesothelioma. As their own letter makes clear, they had previously hinted widely of the possibility that chrysotile may be less pathogenic in the causation of lung cancer—a contention intriguing at the cellular level but absolutely unsupportable on the basis of incontrovertible population evidence. Such human evidence cannot and must not be confused by comments such as "given that smoking is a more powerful factor in lung cancer than asbestos exposure, it is more difficult to define the various roles of different types of asbestos fibers." Moreover, not all of the laboratory evidence of oncogenicity of one fiber compared with another can or should be used as a basis for avoiding the obvious: namely, that a strong dose–response relationship between cancer and chrysotile asbestos exposure is proven and that its slope appears to differ not at all from that of other fiber types. Period. Regarding the differences in pathogenicity of the various fibers in relationship to mesothelioma, I would concur that most reasonable people accept (as I made plain in my annotation) that chrysotile is of lower pathogenicity and may be without potential to cause this disease, although this remains unproven. The reader must be reminded, however, that in developed countries, 100 lung cancers occur for every case of mesothelioma, and despite the close association of the latter disease to asbestos, the public health concern about asbestos cannot be equated with or reduced to its role in causing an extremely rare disease, however scientifically interesting. □

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6. *Stayner and Colleagues Respond*

Langer and Nolan, and Mossman and Gee, express several criticisms of our recent review of the amphibole hypothesis.[1] Langer and Nolan suggested that we failed to present the amphibole hypothesis in a developmental perspective. Our objective was to put this hypothesis in a public health perspective.

The scope of the amphibole hypothesis has been confusing to many, scientists and laypeople alike. We thank Langer and Nolan for reminding us that the hypothesis was first proposed in regard to asbestosis and later extended to mesothelioma. Mossman and Gee[2] may have contributed to this confusion by suggesting that chrysotile may also be less pathogenic than crocidolite in the causation of lung cancer and fibrosis. Therefore, we welcome their statement that the thrust of the amphibole hypothesis is only for mesothelioma. This restriction sharply limits the public health relevance of the hypothesis, since most studies have found that asbestos produces more lung cancers than mesotheliomas.

Langer and Nolan cite several early South African studies as evidence for the hypothesis that crocidolite is more potent than chrysotile in the induction of mesothelioma. We recognized in our paper that "chrysotile *may be* less potent than ... some amphiboles with regards to ... mesothelioma [italics added]"[1(p18)] and cited the most recent report on South African miners.[3] However, the interpretation of these epidemiologic findings is severely hampered by the lack of information on fiber exposure concentrations and dimensions, so no firmer conclusion can be drawn.

Langer and Nolan cite lung burden studies as evidence that tremolite, rather than chrysotile, could be the agent in the induction of asbestosis and mesothelioma. We do not share their enthusiasm for the lung burden studies. Given that chrysotile has a lung half-life of a few months and that mesothelioma has a latency period on the order of 20 to 30 years, it is unlikely that the chrysotile fibers found at autopsy are a meaningful indicator of historical exposure to chrysotile. As an analogy, if we failed to find cigarette smoke in the lungs of a deceased ex-smoker, should we then conclude that cigarettes could not have caused the death?

Mossman and Gee complain that our review failed to cite conference reports "endorsing the amphibole hypothesis." However, the publications they cited generally involved issues of asbestos exposure in buildings and were not pertinent to occupational exposures to chrysotile, which was the subject of our paper. We did cite papers from one of the proceedings[4] that they referred to; in fact, the first reference in our paper, to an article by Pigg,[5] was from this workshop.

Mossman and Gee misquote us as stating that the experimental evidence for the increased pathogenicity of crocidolite is primarily derived from in vitro studies; in fact, we stated that it comes primarily from lung burden studies. They also state that we failed to recognize dozens of references that support the role of superoxide radicals and the increased pathogenicity of amphiboles relative to chrysotile. We note that the BéruBé et al. study[6] that they mentioned was published a month after our own paper. Although we are aware of the additional mechanistic studies referred to, we would argue that theories based on mechanistic arguments, however attractive, must give way to substantive empirical evidence. In this case, the epidemiologic and toxicologic evidence for the pathogenicity of chrysotile is overwhelming.

Finally, Mossman and Gee suggest that critical reviews and annotations should be written by scientists in the "mainstream of relevant panels and scientific meetings." We find this suggestion bizarre. Our own experience in this area is substantial. One of us (RA Lemen) has been active in this area for more than 25 years, has authored numerous scientific papers on asbestos (including a book[7]), was the principal drafter of the International Agency for Research on Cancer's monograph on asbestos, and has testified on asbestos issues to the US Congress and the US Department of Labor on numerous occasions. Another one of us (LT Stayner) has participated in several recent asbestos-related meetings, including a World Health Organization task force on this issue. Frankly, we had hoped that the fact that some of us do not have a long track record in this area would bring a fresh perspective to the debate. We suggest that critical reviews should be written by scientists who are willing to examine all of the relevant data critically, whether or not the data support their own beliefs. We have endeavored to do just that. □

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Integrating HIV Prevention, STD, and Family Planning Services

1. The Availability of HIV Services at Different Types of Clinics: A Survey

We concur with Zena Stein's observations and concerns regarding the separation of services for family planning, sexually transmitted disease, and acquired immunodeficiency syndrome (AIDS), as voiced in her editorial.[1] Recent preliminary animal data suggesting that Depo-Provera—the injectable hormonal contraceptive used widely in the United States and in the developing world—may increase vaginal permeability to HIV under-