



## Asbestos Findings Questioned

Brody's review (1) in part relies on his own work (2) in which he studied the effects of chrysotile asbestos on the proliferation of certain lung cells. In his introduction (2), he relates his laboratory work to situations in which "both workers and local inhabitants . . . of old buildings . . . could inhale large number of fibers." Using rats exposed to several million fibers per liter of air, he found fourfold increases in the percentages of radiolabeled epithelial and interstitial cells between 12 and 48 hr after exposure. He then goes on to state "normal labeling" returned by 8 days after exposure and was maintained through the 1-month period."

Reading both this paper (2) and the review in *EHP* (1), one is led to conclude that Brody regards this as a meaningful experimental analogue for human exposures to airborne asbestos. Though improper work practices can cause transient exposures of less than several thousandths of his experimental levels, "local inhabitants" in buildings have been shown to be exposed to levels less than 1 fiber/l of air (3).

The more serious interpretive flaw is the selectivity with which Brody emphasizes the transient cellular proliferation. Brody's own data show how well his beloved rats deal with the onslaughts of these typhoons of asbestos fibers. At eight days, peace and tranquility return! To me, the news is *not* the wholly predictable transient cellular response, but the stunning effectiveness of the lung defenses. Brody has elsewhere co-authored a generally excellent review of asbestos-related lung biology, but in this instance he misses the point of his own work! Other work also employs huge exposures and finds only very minimal effects in vascular cells one month later (4,5).

Finally, Brody quotes Bates's (1) opinion on mesothelioma causation. While Bates must surely be among the most distinguished Canadians in the field of respiratory medicine, perhaps he will permit me, as one of his former fellows, to refer to some comments on his views on asbestos-related diseases (6).

J. Bernard Gee

Yale University  
New Haven, Connecticut

## REFERENCES

1. Brody AR. Asbestos-induced lung disease. *Environ Health Perspect* 100:21-30(1993).
2. Brody AR, McGavran PD, Overby LH. Brief

inhalation of chrysotile asbestos induces rapid proliferation of bronchiolar-alveolar epithelial and interstitial cells. In: Non-occupational exposure to man-made mineral fibers (Bignon J, Peto J, Saracchi R, eds). IARC Scientific Publication no 90. Lyon:International Agency for Research on Cancer, 1988;102-108.

3. HEI. Asbestos in public and commercial buildings. Literature review and synthesis of current knowledge. Cambridge, MA:Health Effects Institute, 1991.
4. Brody AR, Overby LH. Incorporation of tritiated thymidine by epithelial and interstitial cells in bronchiolar-alveolar regions of asbestos-exposed rats. *Am J Pathol* 134:133-140(1989).
5. McGavran PD, Moore LB, Brody AR. Inhalation of chrysotile asbestos induces rapid cellular proliferation in small pulmonary vessels of mice and rats. *Am J Pathol* 136:695-705(1990).
6. Gee JBL. Asbestos: the turbulent interface between science and policy (letter to the editor). *Can Med Assoc J* 145:14-16(1992).

## Response

Gee has raised an excellent point in criticizing my recent review (1). He has taken issue with the use of our animal studies as a meaningful analogue for human exposures. Such analogies often are problematic, and perfect animal models are hard to find for any disease process. Asbestos-related diseases are no exception, and Gee's concerns are legitimate. However, rats, mice, hamsters, and sheep all develop the same asbestos-related diseases as humans, and investigators are forced to extrapolate from what is seen in an experimental setting to what is known about the process in humans. Thus, in my studies, rats and mice are exposed to high concentrations of fibers for brief periods (one hour to three days) to produce a rapidly developing fibroproliferative process that can be studied from the moment the fibers reach the alveolar surface (2-4). If the disease the animals develop exhibits the same cellular details as those in humans, a number of reasonable postulates can be tested regarding the molecular and biochemical mechanisms involved.

I have suggested that when humans are exposed, the initial responses at the alveolar level are essentially the same as those recorded in animals (1). Of course, we cannot observe these events in people, and we certainly do not know how many fibers will reach the alveolar and pleural surfaces of exposed humans. My experimental animals receive high concentrations as have many occupationally exposed individuals. People in buildings with asbestos-containing materials could be exposed as well, surely to much lower concentrations of

fibers, but possibly for longer periods of time and more frequently than the experimental animals. Since it is difficult to monitor peak exposures and to know what an individual's exposure history will be, I support the cautious view proposed by a number of individuals actively working in the fields of industrial hygiene and risk assessment (5-7).

It seems that Gee has failed to recognize that the "transient cellular proliferation" which he dismisses goes on to result in a scar that persists for at least six months after a brief exposure. The scar is composed of collagen and fibronectin as well as increased numbers of smooth muscle cells, fibroblasts, and macrophages, along with thickened walls in small vessels (4,8). Where do these increased populations of cells come from if not from the proliferative events we and others have recorded? Gee makes light of a brief proliferative response at a critical anatomic site in the lung, but he should take note of the legacy of these dividing cells, because these cells are the source of the initial lesions of asbestosis, and they are teaching us something about the mechanisms of fibroproliferative disease in general. I have been accused of making "interpretive flaws" in my review. While I am sure that I have committed such flaws in many settings, treating a transient proliferative response as significant in leading to interstitial disease probably is not one of them. If our animals are exposed for three days, the increases in proliferation can be measured through the following week as a prominent lesion develops. Is this still a meaningless transient response? If an individual were exposed to peak bursts of fibers for 15 minutes or an hour a day, two days a week for two years, and if every time an aliquot of the fibers reaches the alveolar surface or pleural membranes cell division is activated, who is to say this is not a significant event in the future of that person? [See discussion of cell division and neoplasia in Brody (1).] While the "stunning effectiveness" of lung defense mechanisms is readily observed in our experimental animals, it should be obvious to even the casual reader that these defenses are not entirely effective. If one or three hours of exposure to asbestos causes cell proliferation and consequent scar formation in the lungs of rats and mice (1-4,8), what evidence does Gee offer to ease concerns about potential development of disease in the lungs of individuals who are exposed day after day to unknown concentrations of fibers? It is

my view that the proliferative response (transient with brief, intense exposures; prolonged with repeated exposures) is key to the development of disease.

Gee has referred to two of our papers as employing "huge exposures" and finding "only very minimal effects in vascular cells." First, he has ignored the fact that the exposures, while high in fiber number, are very brief (one hour or three hours). As a result, the count of accumulated fibers in the lung does not approach the numbers necessary to compromise normal clearance pathways (9), but the lesions develop nonetheless, as discussed above. Second, the effects Gee refers to are hardly "minimal," and he misrepresents our findings as taking place only in vascular cells. Although he cited the paper, Gee apparently has not thoroughly read the article I co-authored with Overby (2), inasmuch as no mention of the vasculature is made in that paper. In another paper cited by Gee, my co-workers and I showed that one month after the brief exposure, there were twice as many smooth muscle cells, and the vessel walls were doubled in thickness (4). Ultrastructural morphometry (8) also showed over 500% increases in the cellular and matrix volumes of the developing interstitial lesions one month after only one hour of exposure. These data have led me to conclude that "peace and tranquility" do, in fact, not return to the lungs of my "beloved rats," nor to my beloved mice, and probably not to the lungs of people with significant exposures such as custodians and maintenance workers who are repeatedly exposed to fibers released from asbestos-containing materials.

**Arnold R. Brody**  
Tulane University Medical Center  
New Orleans

#### REFERENCES

1. Brody AR. Asbestos-induced lung disease. *Environ Health Perspect* 100:21-30(1993).
2. Brody AR, Overby LH. Incorporation of tritiated thymidine by epithelial and interstitial cells in bronchiolar-alveolar regions of asbestos-exposed rats. *Am J Pathol* 134:133-140(1989).
3. McGavran P, Brody AR. Chrysotile asbestos inhalation induces tritiated thymidine incorporation by epithelial cells of distal bronchioles. *Am J Respir Cell Mol Biol* 1:231-235(1989).
4. McGavran PD, Moore LB, Brody AR. Inhalation of chrysotile asbestos induces rapid cellular proliferation in small pulmonary vessels of mice and rats. *Am J Pathol* 136:695-705 (1990).
5. Altree-Williams S, Preston JS. Asbestos and other fiber levels in buildings. *Ann Occup Hyg* 29:357-366(1985).
6. Cohen N. Regulation of in-place asbestos-containing material. *Environ Res* 55:97-106 (1991).
7. Oliver CL, Sprince NL, Greene R. Asbestos-related radiographic abnormalities in public school custodians. *Toxicol Ind Health* 6:629-631(1990).
8. Chang L, Overby LH, Brody AR, Crapo JD. Progressive lung cell reactions and extracellular matrix production after a brief exposure to asbestos. *Am J Pathol* 131:156-170(1988).
9. Coin PC, Roggli VL, Brody AR. Deposition, clearance and translocation of chrysotile asbestos from peripheral and central regions of the rat lung. *Environ Res* 58:97-116(1992).

#### NAFTA and U.S. Agriculture

Contributing editor Daniel VanderMeer repeats a flawed picture of the position of U.S. agriculture on the North American Trade Agreement ["NAFTA Prompts Health Concerns across the Borders," *EHP* 101(3)].

A few groups of specialty crop producers have expressed either reservations or oppo-

sition to NAFTA. However, the overwhelming majority of U.S. agricultural producers, handlers, processors, and marketers have endorsed the agreement. These groups, organized by "AG for NAFTA," are listed in Table 1. We have joined this group, convinced that NAFTA will promote the growth of both bulk and high-value U.S. farm and food exports, create domestic jobs, and provide Mexico with the opportunities it needs to modernize its economy, its labor market, and its system of environmental protection.

**Kyd D. Brenner**  
Corn Refiners Association, Inc.  
Washington, DC

**Table 1.** AG for NAFTA members as of 15 July 1993

A.E. Staley Manufacturing Company	Louis Dreyfus Corp.
Affiliated Rice Milling, Inc.	Mid-America Dairymen, Inc.
The Agribusiness Council	Millers' National Federation
The Agricultural Policy Working Group	Monsanto Agricultural Group
Agricultural Processors, Inc.	National American Wholesale Grocers' Association
American Farm Bureau Federation	National Broiler Council
American Feed Industry Association	National Cattlemen's Association
American Oat Association	National Corn Growers Association
American Maize-Products Company	National Grain and Feed Association
American Rice, Inc.	National Grain Sorghum Producers
American Seed Trade Association	National Grain Trade Council
American Meat Institute	National Grange
American Soybean Association	National Oilseed Processors Association
Archer Daniels Midland	National Pork Producers
Beaumont Rice Mills, Inc.	National Sunflower Association
Blue Diamond Growers	North American Export Grain Association
Broussard Rice Mill, Inc.	Northwest Horticultural Council
Bryan Forwarding Company, Inc.	Pekin Energy Company
The Bunge Corporation	Pioneer Hi-bred International
Coastal Rice and Futures, Inc.	Printpack, Inc.
Chicago Board of Trade	Producers Rice Mill, Inc.
Co Bank-National Bank for Cooperatives	Rain and Hail Insurance Service
Collingwood Grain Co.	Ralston Purina Co.
ConAgra, Inc.	The Rice Belt Warehouse, Inc.
Connell Rice and Sugar Co.	The Rice Company
Cormier Rice Milling Co., Inc.	Rice Growers Association of California
Corn Coalition	Rice Millers' Association
Corn Refiners Association	Riceland Foods, Inc.
Creed Rice Company, Inc.	Rice Tec, Inc.
Drexel Chemical Company	Rivana Foods, Inc.
FMC Corporation	Smoot Grain Company
Falcon Rice Mill, Inc.	Sortex-Scancore, Inc.
Farmers Grain Terminal, Inc.	Southern Cotton Oil Co.
Farmers Rice Milling Company, Inc.	Southern States Cooperative
Farmland Industries, Inc.	Sunkist Growers
Great Western Malting Company	Sunwest Milling Company Supreme Rice Mill, Inc.
Grocery Manufacturers of America	Tabor Grain Company
Growmark	Taylor-Cross International
Inchcape Testing Services	United Egg Association
Incotrade, Inc.	United Egg Producers
Land O'Lakes	Washington Apple Commission
Langston Companies, Inc.	Wetsel Seed Company
Liberty Rice Mill, Inc.	

## Methyl Ethyl Ketone and Methyl Isobutyl Ketone Not Carcinogenic

The April 22, 1993, issue of *Environmental Health Perspectives* contained a commentary by Legator and Strawn entitled "Public Health Policies Regarding Hazardous Waste Sites and Cigarette Smoking: An Argument by Analogy." Although the article does not include any discussion of either methyl ethyl ketone (MEK) or methyl isobutyl ketone (MIBK), it does list them in Table 3 as substances that cause cancer in animals and/or humans."

Because MEK and MIBK are both widely used industrial chemicals, they have been studied extensively for possible human health or environmental effects. The Ketones Panel of the Chemical Manufacturers Association has sponsored a number of the studies and surveyed all the pertinent literature on these two compounds. The panel is not aware of any evidence suggesting that either MIBK or MEK causes cancer in humans or animals. Indeed, neither MEK nor MIBK is known or reasonably expected to cause any type of chronic health effect in humans.

MEK has been shown to be inactive in a wide variety of *in vitro* and *in vivo* genetic toxicity assays and was not neurotoxic in five recent studies. Although MEK has not been tested specifically for carcinogenicity, the data on its structure and metabolism, the results of numerous subchronic studies, and the absence of genotoxicity indicate that MEK is highly unlikely to pose a cancer risk.

With respect to MIBK, inhalation studies conducted with rats, mice, dogs, and monkeys all indicate a very low order of subchronic toxicity. The results from a number of different mutagenicity screening assays show that MIBK exhibits very little, if any, mutagenic activity. Existing studies also demonstrate that MIBK is not teratogenic and exhibits low reproductive toxicity. As with MEK, MIBK has not been tested specifically for carcinogenicity because data on its structure and metabo-

lism, subchronic health effects, and genotoxicity indicate that it is highly unlikely to pose a cancer risk.

If you are aware of any evidence that either MEK or MIBK is carcinogenic, please notify the panel. If not, we request that you publish a correction in order to set the record straight. Inaccurate and misleading information, even from a single publication, can have a significant impact. We therefore ask that you take the steps necessary to correct the false impression that has been created by your April 22, 1993, publication.

If you have any questions or wish to provide information on either of these these compounds, please contact Barbara Francis, manager of the Ketones Panel, at (202) 887-1314.

**Gordon D. Strickland**

Chemical Manufacturers Association  
Washington, DC

### Response

I am grateful to Gordon Strickland for detecting an error in my commentary in the April 22, 1993, issue of *Environmental Health Perspectives*. To my knowledge, there have been no carcinogenesis studies carried out with methyl ethyl ketone (MEK) in animals. I am aware of only a single unconfirmed study (1) that indicated a statistically significant increase in buccal or pharyngeal neoplasms. The Xs in Table 3 were inadvertently placed in the category for cancer for both MEK and methyl isobutyl ketone when they should have appeared under the heading "neurological."

**Marvin S. Legator**

University of Texas Medical Branch  
Galveston, Texas

### REFERENCE

1. Alderson M, Rattan N. Mortality of workers on the isopropyl alcohol plant and two MEK dewaxing plants. *Br J Ind Med* 37:85-89 (1980).

*Editor's Note: We regret our error in Legator and Strawn's Table 3 and any confusion this error may have caused. The corrected table is shown below.*

## Breast Cancer and Menarche in Asian Women

Fortunately for women, the scientific community is finally beginning to become more serious about breast cancer. Because of the recognized association between estrogen exposure and breast cancer, two recent discussions have suggested that lower risk in Asian women may be related to later onset of menses. It has been stated that Chinese women begin menses at an average age of 17 (1,2). This statement, which occurs in both *EHP* and *Science*, is unreferenced in both and is contrary to published studies.

Eveleth and Tanner (3) have summarized studies finding that well-off Chinese girls from Hong Kong and Singapore begin menses around age 12.4. A recent study from mainland China including 162,902 Han girls (4) found that the median age of menarche was 13.17 years for urban girls and 13.83 years for rural girls. Therefore, the lower rate of breast cancer in Asian women must not be related to a late age of menarche since studies find that Asian girls begin menses about the same time as girls in many other cultures (3).

At any rate, age of menarche may not be as good a marker of estrogen exposure as age of onset of breast development. The length of time between the onset of development and the beginning of menses may differ in various populations and could be an important factor in breast cancer epidemiology. In general, many studies on the prevalence of secondary sexual characteristics in girls start with subjects at too late an age (for example age 8, 10, or even 12) to establish the timing of onset (5,6). Better understanding of women's natural growth and development cycles is necessary for the develop-

**Table 3.** Effects of substances found in cigarette smoke (16) and at a hazardous waste site (18,19)

Chemical	Cancer	Developmental	Liver/ kidney	Neurological	Blood	Lung	Cardiovascular
Arsenic	X	X	X		X	X	X
Cadmium	X	X	X			X	X
Chromium	X		X			X	
Lead	X	X		X			X
Nickel	X	X				X	
Benzene	X	X	X	X	X		
Toluene		X	X	X			
Xylene		X		X			
Tetrachloroethylene	X	X	X	X			X
Trichloroethylene	X	X	X	X			
Methyl ethyl ketone			X	X	X		
Methyl isobutyl ketone			X	X	X		

ment of practical public health cancer prevention strategies.

**Marcia E. Herman-Giddens**  
 Duke University Medical Center  
 Durham, North Carolina

**REFERENCES**

1. A holistic approach to breast cancer research. *Environ Health Perspect* 101:116-120(1993).
2. Marshall E. Search for a killer: focus shifts from fats to hormones. *Science* 259:618-621 (1993).

3. Elveleth PA, Tanner JM. *Worldwide variation in human growth*. Cambridge:Cambridge University Press, 1990.
4. Hin HS, Chen JZ, Su JZ, Zhu F-C, Xing W-H, Li J-Y, Ye G-S. The menarcheal age of Chinese girls. *Ann Hum Biol* 19:503-512 (1992).
5. Herman-Giddens ME, MacMillan JP. Prevalence of secondary sexual characteristics in a population of North Carolina girls ages 3 to 10. *Adolesc Pediatr Gynecol* 4:21-26(1991).
6. Herman-Giddens ME, Slora E, Hasemeier C, Wasserman R. The prevalence of secondary sexual characteristics of young girls seen in office practice. 147:455(1993).

*Editor's Note: Fran Pollner's source for the age of menarche in Asian women was a breast cancer review article in the 30 July 1992, issue of The New England Journal of Medicine (Harris JR, Lippman ME, Veronesi U, Willett W. Breast cancer. 327:319-328). Harris et al. cite as their source Chen J, Campbell TC, Li J, Peto R. Diet, life-style, and mortality in China: a study of the characteristics of 65 Chinese counties. Oxford:Oxford University Press, 1990:750.*

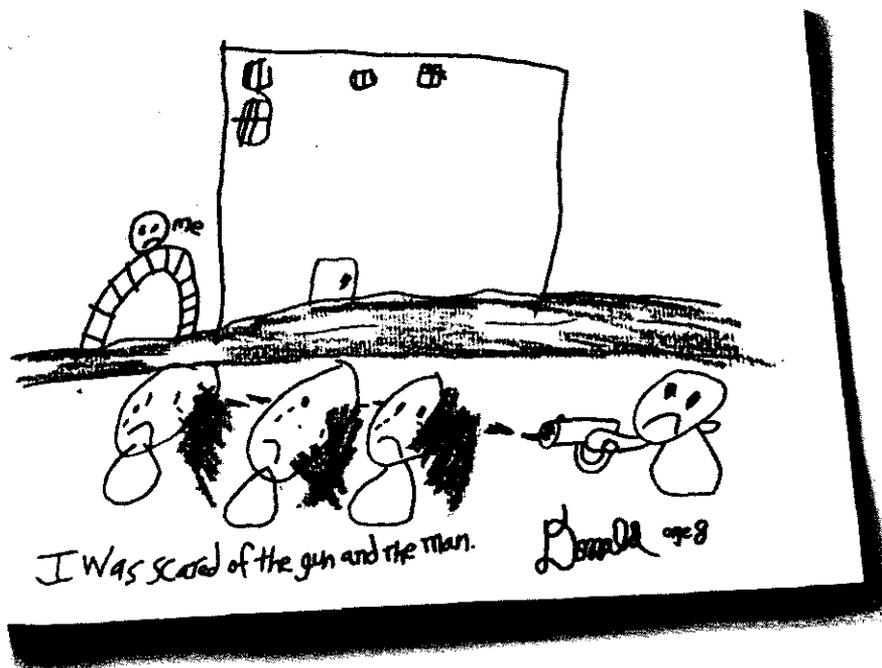
**Children draw**

**what they see,**

**and what they see**

**is a crime.**

courtesy of The Atlantic Monthly



Help redraw their world.  
 Call and get free information  
 on how to protect your children  
 from drugs and violence  
 in your neighborhood.

**Call 1-800-WE PREVENT**

**Ad Council** A Public Service of  
 This Publication

