A recent interpretation of the pathogenetic role of asbestos fiber size in the development of mesothelioma and in the possibility of mesothelioma prevention needs clarification. This point of view is based on a biased interpretation of the literature. Epidemiologic, experimental, and molecular evidence suggests that the arguments for the role of fiber size relative to dose, dose–response effect, and genetic susceptibility are scientifically unsound. Their proponent also states that means available in the past for the implementation of dust-control measures and/or personal protective equipment would not have contributed to reducing the frequency of mesothelioma among exposed subjects, an argument again based on invalid assumptions. Key words: asbestos; mesothelioma; prevention.

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An unsound hypothesis, positing a role for fiber size in the pathogenesis of mesothelioma and debunking the potential effectiveness of dust-control measures that were available by the mid 1980s for its prevention, has recently surfaced in the medical literature. Its author, Chiappino, has arrived at erroneous conclusions based on arbitrary interpretations of selected earlier reports. A danger is that his conclusions, which are not scientifically valid, could be used to support unjustified acquittals of negligent defendants in the courts.

Chiappino’s published interpretations need to be corrected or clarified with respect to:

1. the role of fiber dimensions (length and diameter);
2. the alleged predictability, but not preventability, of mesotheliomas until the 1980s, and role of exposure dose and the dose–response effect;
3. the alleged role of genetic susceptibility in determining the risk of developing mesothelioma; and
4. the alleged uselessness of dust control measures and ineffectiveness of personal respiratory protection equipment for reducing exposures.

The Role of Fiber Dimensions

Chiappino states as a given fact that only “ultrashort” and “ultrathin” asbestos fibers are able to reach the parietal pleura and lead to the development of malignant pleural mesothelioma. His statement is based mainly on three publications that allow him to assert that ultrathin fibers are “the only dimensional size class that can get past the lung–pleura barrier.”

A thorough reading of the papers he quotes reveals that:

According to Paoletti et al., “about 80% (48/60) of the fibers found were under 5 µm in length, and 68% were under 0.3 µm in diameter,” while according to Boutin et al., “a total of 22.5% of fibers were ≥ 5 µm in length in black spots” (the small dot-like spots of the parietal pleura near the lymphatic stomata). In these areas fibers 8 µm or more in length accounted for 8% of all fibers, those 15 µm or longer; 2.1%; and the maximum length recorded was 29 µm; the geometric mean of the diameter was 0.13 µm, greater than that of the fibers found in the lung, which was of 0.10 µm. The conclusions were that “long amphibole fibers concentrate in the same structures of the parietal pleura that trap other particles such as coal dust.”

According to Suzuki and Yuen, “the majority of asbestos fibers detected in the lung and mesothelial tissues were shorter than 5 µm”; in the study published in 2002, the fibers longer than 5 µm represented 10.5%,...
while in a previous study the reached 18.6%. The conclusions were that “such short, thin asbestos fibers should not be excluded from those contributing to the induction of human malignant mesothelioma,” which is very different from saying that they are the sole agent in mesothelioma induction.

Even based on a more recent pathology study, the principle of “contribution”—not of exclusiveness—of fibers that are equal to or shorter than 5 µm in length and equal to or smaller than 0.25 µm in diameter in the development of mesothelioma is confirmed. There is no evidence that only ultrathin and ultrashort fibers penetrate the pleura, since, although the smaller fibers are in the majority, larger fibers are also present in the parietal pleura, both in the material examined in the studies cited by Chiappino and in other studies by the same authors.

Furthermore, the common occurrence in the parietal pleura of “black spots” shows that the lung–pleura barrier is not at all impassable, even for particles much larger than “ultrathin” and “ultrashort” fibers. These parietal pleura agglomerates, which contain carbonaceous pigments and mineral fibers, have been found in 92.7% of 150 consecutive autopsies of inhabitants of urban areas in Belgium.

Chiappino states such findings as “not physiological,” and “likely linked to transitional increases in the permeability of the lung–pleura barrier due to inflammatory events or other situations influencing the direction of the lymphatic flow.” The relevance of such an obvious statement, in respect to asbestos exposure and the consequent induction of mesothelioma, is not clear, since it refers to a phenomenon that certifies is not physiological. It is well known that benign effusions (precisely by pleural transudation and/or exudation) are the first reactive manifestations that might later lead to those features of diffuse pleural fibrosis considered among the indicators of previous exposure to asbestos.

Moreover, Gibbs et al. found long fibers of commercial amphiboles in subjects with diffuse pleural fibrosis, while Dodson et al. have shown the presence of similar fibers in pleural (parietal) plaques of asbestos workers, as well as in the peritoneum and in the mesentery. Starting from the lung, asbestos fibers can reach other organs by direct or macrophage-mediated migration, or by diffusion through the lymphatic and blood vessels. In addition, once they have reached the lung, asbestos fibers can undergo transformation and degradation processes that might result in reducing length and diameter.

Our concerns about Chiappino’s statements are also supported by other scientists conclusions:

Asbestos fibers of all lengths induce pathological responses and caution should be exerted when attempting to exclude any population of inhaled fibers, based on their length, from being contribu-

cors to the potential for development of asbestos-related diseases.

Clearly, fibers of the type and size known to be associated with the greatest risk of mesothelioma do, in fact, migrate to pleural tissues.

The large majority of fibers detected in the omentum and mesentery of 20 occupationally exposed workers suffering from mesothelioma, inclusive of three shipyard workers affected by peritoneal mesothelioma, were longer than 5 µm, so that Chiappino’s view is definitely not valid for peritoneal mesotheliomas, representing about 10% of all mesotheliomas.

**Alleged Predictability, but Not Preventability, of Mesothelioma until the 1980s, and the Role of Exposure Dose and Dose–Response Effect**

The first scientific articles on the carcinogenic effect of asbestos on the mesothelium appeared in the 1960s, on the basis of clinical evidence in exposed workers. In 1964, the conference on the biological effects of asbestos organized by the New York Academy of Sciences ratified the general consensus of the scientific community on the carcinogenic effects of asbestos. In that conference the first cases of pleural mesothelioma in asbestos workers in Italy were described and presented by Professor Vigliani, who had been Chiappino’s professor at the University of Milan. In 1977, the IARC classified all types of asbestos in the group of known human carcinogens. In the 1960s, asbestos-exposed subjects were already under mandatory health surveillance by occupational physicians in many countries, including Italy. No occupational physician, therefore, from the mid 1960s onwards, could be unaware of the carcinogenic effect of asbestos on the mesothelium, and consequently of the need to give indications to those in charge within the companies of the rigorous measures of environmental prevention and individual protection that were needed.

Chiappino states that the means for prevention that could have been applied before the 1980s to eliminate or reduce the risk related to exposure to dusts were efficient to prevent asbestosis, which is caused by inhaled fibers of all dimensions, but not mesothelioma, which is caused, he repeatedly emphasizes, exclusively by ultrathin fibers. The inconsistency of this argument is shown above.

It has been repeatedly claimed that mesotheliomas can be caused by light and/or brief exposures. A cut-off “in the region” of 5 fibers/mL of air/year was suggested for amphiboles. However, in a later, ample epidemiologic survey carried out in France, a significant excess of mesotheliomas was observed for levels of cumulative exposure as low as 5 f/mL/year or lower, below the limits of acceptable exposure adopted in many industrial countries in the 1980s. The IARC stated, as early as 1977, that there is no proof of a cut-off level of
exposure to asbestos below which there is no risk,1 a statement that was repeated by Doll and Peto in 198533 and, more recently, citing Selikoff,34 by Motley et al.35

Some authors have declared themselves in favor of recognizing a cut-off level on the basis of the assumed levels of exposure of asbestos-related mesothelioma cases,36 but according to Hodgson and Darnton37 the direct confirmation of a threshold based on human data is virtually impossible, and case–control studies with measurement of pulmonary asbestos content38–40 do not suggest any threshold, or any tendency of the steepness of the dose–response curve to decrease at the lower ends of their scales of exposure.

At the end of the 1960s, it was already evident that increased risks of mesothelioma correlate with increases in both intensity and duration of exposures to asbestos, and thus with the overall dose of inhaled fibers,31–43 and that lower cumulative doses lead to longer latency periods for the onset of mesothelioma. This observation has led to the consideration that a reduction in dose, i.e., applied prevention, will at least postpone the appearance of mesothelioma.43–46

Later, the HSE’s asbestos workers’ mortality survey in England and Wales demonstrated that workers first exposed to asbestos before the implementation of the 1969 Regulation, and thus exposed to higher intensities than thereafter, had a higher frequency of mesothelioma than those first exposed only after 1970, showing that “prevention,” intended as a reduction of intensity of exposure, reduces the occurrence of mesotheliomas.42

These observations then found authoritative confirmation, and finally a computation of risk according to dose and latency.48,49 The doubts raised by some authors50 about the existence of a dose–response relation for mesothelioma refer to particular case studies, often characterized by very high exposures, whereas Peto’s formulas answer the majority of observations and are almost unanimously supported by the scientific community. More recently, other authors51 observed a significant dose–response correlation for pleural mesothelioma in a cohort of 5,000 Londoners exposed to asbestos between 1933 and 1980. Various authors have verified a significant increase in the risk of mesothelioma correlated with the increase in pulmonary asbestos content detectable by electron microscopy.52–55

The epidemiologic findings are also confirmed by experimental studies showing that a reduction in dose lengthens the period of latency of mesotheliomas, and in this way reduces their incidence, since the duration of latency exceeds that of the life of rats.56,57 In-vitro studies58 of the damaging effect of asbestos corpuscles on DNA, which is strongly inhibited by the chelating action of the leukocytes, also supports the relevance of continuous inhalation of “fresh” fibers for the onset of mesothelioma.

Chiappino emphasizes the role of the “trigger dose” as a short-lasting and irreversible phenomenon in pleu-
available at that time in occupational settings." He postulates that a systematic error was introduced in the field of industrial hygiene when it was decided to consider only fibers "subject to regulation," neglecting all those under 0.5 µm in diameter, which, instead, are in his view the ones solely responsible for biological reactions. He also claims, paradoxically, that air extractors with filters unable to stop the ultrathin fibers were responsible for disaggregating the large asbestos fibers, thus increasing the risk proportionally to their power. This is meant to give credit to the statement that mesothelioma is caused only by ultrathin fibers that could not have been controlled with the air-treatment technology available in 1960–1980. With these statements, Chiappino seems to be unaware of what the real situation was like in work environments in those years, and introduces misleading elements concerning the characteristics of the air extractors.

Inside the workshops that had large amounts of dust, wall-mounted air extractors were installed to expel polluted air directly outside, with no filtering system at all. Some of these air extractors were still visible a few years ago in old dismantled industrial sheds (e.g., Eternit in Casale Monferrato, Breda in Pistoia, Italy). These systems were based on dilution ventilation. The introduction of filtering systems, usually fabric dust collectors, needed outdoor installation.67 There was neither need nor convenience in recycling exhausted air in workshops without heating or air conditioning.

The 1970 edition of the manual Industrial Ventilation states, with regard to the recirculation of exhaust air:

Air recycling is not recommended in the cases where the extractor systems treat substances that have an effect on the worker's health. Recirculation is accepted if the contaminants that are filtered are simply bothersome and do not pose a real health threat, and in any case only during the winter period in order to save on the cost of heating.68

Contrary to what Chiappino asserts, HEPA (high-efficiency particulate arrestance) filters, which were developed in the 1940s by the U.S. Atomic Energy Commission to respond to the need for an efficient filtering of radioactive particulate contaminants, were commercially available in Italy at the beginning of the 1950s. In addition, their use was the filtering the air that was released into the environment. They would not have had any role, therefore, in protecting the workers in the working environment. Air extraction at the source, physical confinement of the polluting source for limiting the air dispersion of pollutants, the so-called “close-cycle,” if at all reasonably possible, has always represented the criterion of choice for selecting dust-control measures in workplaces. Consequently, prevention has always been based on extraction and expulsion of polluted air, and not on its filtration.

Furthermore Chiappino asserts, without citing any supporting reference, that personal protective equipment was ineffective for respiratory protection. Indeed, filters do not work as "sieves," but they are able to stop particles and fibers of much smaller sizes than those indicated by the manufacturer as filtering capacity. This happens because very small fibers and particles tend to deposit around the openings between the threads of the filtering fabric for diffusional and electrostatic reasons, giving more protection than that which could be expected from a simple "sieve" effect.69–72

In conclusion, Chiappino’s argument basically rests on two points. 1) pleural mesothelioma is induced by the ultrathin and ultrashort fibers only; and 2) asbestos persistence in human tissues is extremely long compared with other known carcinogens.

With regard to the former, several studies provide evidence that fibers of all lengths and diameters play a role in the induction of mesothelioma. With regard to biopersistence, the recognition of this property is used by Chiappino to exclude the need of repeated and prolonged exposures to initiate and promote the carcinogenesis that will lead to the development of mesothelioma. All epidemiologic, experimental (in vivo and in vitro) and molecular evidences, however, reject this pathogenetic hypothesis, as well as the negative impact its acceptance would have in terms of actual prevention and regulations worldwide. It would actually mean the total acquittal of anyone who, being in a position to do so, omits to take care to prevent asbestos exposure, or at least reduce its intensity, leaning on “fatalistic principles” that are not substantiated in the international scientific literature.

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