

# Asbestos-Related Research: First Objectivity then Conclusions

**Keywords:** Chrysotile; Amphiboles; Asbestos; Mesothelioma; Lung cancer

## Abstract

Asbestos-related risks have been extrapolated from the past, when high-dose occupational exposures were frequent. The linear no-threshold dose-response pattern has been assumed, but its applicability to low-dose asbestos exposures has never been proven. Morphologically, malignant mesothelioma can resemble various cancers. There are diagnostic algorithms; however, a tumor diagnosed by standard methods as mesothelioma is not a well-defined entity, in all cases substantially different from other cancers. Well-aimed search and screening effect have probably contributed to the enhanced incidence of mesothelioma and other asbestos-related diseases in exposed populations. Asbestos-related diseases have been extensively studied in Russia. The prevailing view is that, if all precautions are observed, modern technologies of asbestos production and processing are acceptably safe, whereas bans and prohibitions applied by some countries are excessive. At the same time, there are economic interests to promote chrysotile. Biases due to industrial interests have compromised the objectivity of some asbestos-related reports. In the author's opinion, the "all fibers equal" basis of official regulations can be accepted provisionally pending objective and reliable evidence on toxicity of different asbestos types and man-made substitutes. On the basis of independent scientific data, the bans and restrictions on asbestos in some countries should be re-examined and potentially revised. Any permit of continued production or use of asbestos materials must be coupled with regulations and efficient measures to prevent environmental contamination associated even with minimal additional risks.

Asbestos-related risks have been estimated on the basis of extrapolations from the past, when high-dose occupational and non-occupational exposures were frequent. Evolution of the concept of low- vs. high-dose asbestos exposures can be illustrated by the gradual decline of the Permissible Exposure Limit (PEL) adopted by the Occupational Safety and Health Administration (OSHA): 1971-12 f/cc of air as a 8 h time weighed average; 1972- 5; 1976-2; in 1986, the current PEL for asbestos in the workplace was established: 0.1 f/cc [1,2]. A well-known asbestos contamination was the "Mr Fluffy" incident in Australia (1960-70s), where loose asbestos was used for insulation of houses [3]. In Russia, corrugated asbestos board has been broadly used for roofing being often sawed by hand; asbestos-cement pipes are routinely used for drinking water distribution (Figure 1) [4]. Other asbestos-containing materials (flat sheets, asbestos paper, cloth, gaskets, etc.) are broadly used now as before. The linear no-threshold dose-response pattern has generally been assumed for the low exposure levels, but its applicability to low-dose asbestos exposures has never been proven. In some places, asbestos fibers are present in the natural environment due to erosion of surface deposits. For example, the fibers were detected in the lungs of 63.6% deceased individuals from the general population [5]. Inhalation and discharge of the fibers occur normally [6], probably within a dynamic equilibrium. Existence of a threshold for the exposure to mineral fibers has not been reported, but may be assumed by analogy with other environmental factors that have induced evolutionary



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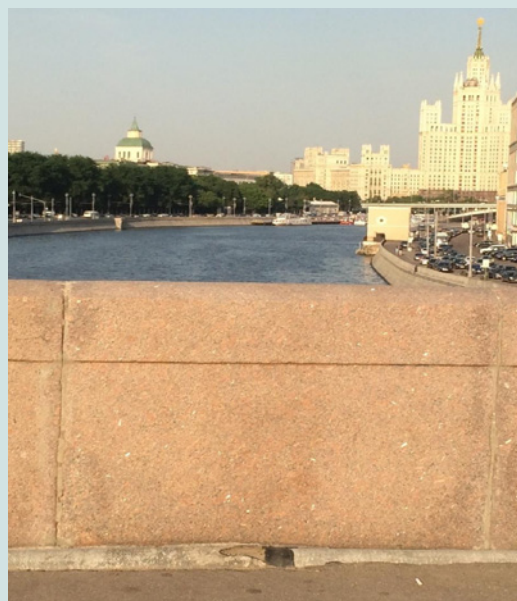
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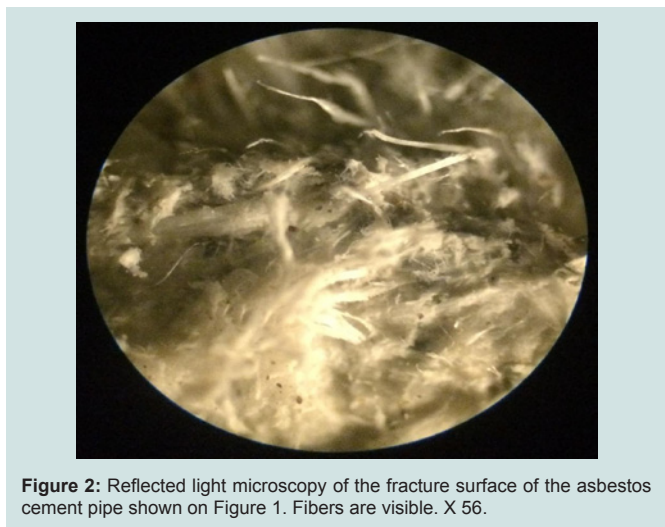
adaptation [7,8]. Further research into non-linear, threshold cancer risk models is warranted both for asbestos [9], and for its substitutes.

Apparently, the screening effect has contributed to the enhanced registered incidence of asbestos-related diseases in exposed populations and an over estimation of the dose-response relationship. In particular, mesothelioma (Mt) was sought among exposed people and correspondingly more often found. Malignant Mt is an uncommon neoplasm developed by a small percentage of people exposed to asbestos. It can be spontaneous, or occur when asbestos fibers are present in the pulmonary or pleural tissues. Apart from asbestos, other potential etiologic factors of malignant Mt are mineral (erionite) and artificial (ceramic, carbone nanotubes) fibers [10-13], virus SV40, radiation, and genetic predisposition [14-17] (Figure 2).

Misclassification of disease is a problem for several of the cancer



**Figure 1:** Partly destroyed asbestos cement drain-pipe in Moscow.



**Figure 2:** Reflected light microscopy of the fracture surface of the asbestos cement pipe shown on Figure 1. Fibers are visible. X 56.

sites. This is particularly true for mesothelioma, which did not have diagnostic category in the ICD system until the 10<sup>th</sup> review was initiated in 1999 [18]. Histologically, malignant Mt can resemble various cancers and the lack of accurate biomarkers makes diagnosis challenging [19]. Some Mt studies may have mistakenly included tumors having similar morphology [17]. Metastatic cancers can undergo structural transformation, becoming histologically similar to malignant Mt [20]. The morphological differential diagnosis is different depending on Mt subtype [21]. There are standard diagnostic algorithms-a tumor diagnosed as malignant Mt through standard methods is not a well-defined entity, in all cases substantially different from other cancers. Cytogenetic studies found out that malignant Mt has complex and even chaotic chromosomal aberrations [14,22,23]. No marker discriminates well between Mt and other cancers [19,24], which, in conjunction with uncertainty about progenitor cells [14], makes the demarcation of Mt as an entity indistinct. Mesothelin and osteopontin have been considered promising markers, but both have limitations [18,25,26]. Although several studies indicated that mesothelin is useful for screening, other evidence indicates that this marker has a considerable false-positivity rate [27], being insufficiently sensitive for early diagnostics [28]. Osteopontin serum concentration is not regarded to be an adequate marker because it lacks specificity in differentiation between Mt and metastatic carcinoma [29]. Data on microRNA down regulation in Mt, compared to lung cancer [30,31], may be promising for demarcation, but since microRNAs are often deregulated in different cancers [31,32], the specificity of this marker is questionable, and the possibility of misclassifications cannot be excluded [33]. The validity of biomarkers is sometimes over estimated due to the push by researchers, institutions and sponsors for ground-breaking research [28]. In Russia, certain studies of reportedly specific markers, e.g. of cell damage by alcohol, were never confirmed by later research, and resulted from organ biopsies performed without sufficient clinical indications [34].

Furthermore, biases can be encountered in Mt and asbestos research, e.g. the detection of small amounts of fiber in pulmonary or pleural tissues automatically attributing the neoplasm to asbestos [35]. As mentioned earlier, asbestos fibers are not infrequent in pulmonary tissues of people without any professional exposure [5]. Some studies

rely on work histories of questionable reliability, interviews with relatives of deceased patients, etc. Biases due to industrial interests and litigation may further compromise objectivity [35].

Asbestos-related diseases have been extensively studied in Russia. The prevailing view is that, if all precautions are observed, modern technologies of asbestos production and processing are acceptably safe, whereas bans and prohibitions applied by some countries are excessive [36,37]. Some scientists admitted that the concept of much higher carcinogenicity of the amphiboles compared to chrysotile has not been confirmed [38]. There are also strong economic interests to promote chrysotile. Accordingly, statements in favor of chrysotile (sometimes without references) can be encountered [39,40]: “Chrysotile fibers are easily dissolved and discharged” [40]. Papers by David Bernstein agree with some Russian reports:

- Following short-term exposure the longer chrysotile fibers rapidly clear from the lung and are not observed in the pleural cavity. In contrast, short-term exposure to amphibole asbestos results quickly in the initiation of a pathological response in the lung and the pleural cavity [41];
- Chrysotile fibers are rapidly cleared from the lung in marked contrast to amphibole fibers which persist [42].

It should be noticed that the fiber presence is essential in pulmonary and pleural tissues, not in the cavity. Given the possibility of a post-depositional movement of chrysotile fibers from the lung to the pleura [43-48], such statements are an over simplification. The rate of asbestos retention cannot be characterized only on the basis of measurements of fiber contents in pulmonary tissues - The proportion of chrysotile fibers (as opposed to the amphiboles) was shown to be higher in parietal pleura than in lung tissue [43]. Moreover, the accelerated clearance of chrysotile from the lung can be partly caused by a disintegration of chrysotile (but not amphibole) fibers into thin fibrils, which are more difficult to identify. The total number of fibrils would increase due to fiber splitting [47,49,50], possibly together with the carcinogenic effect, as the split fibrils can move to the pleura [45,47,48]. Asbestos fibers have been identified in the pleura by autopsy, chrysotile being the predominant asbestos form found in pleural plaques [51] and pleural/mesothelial tissues in general [46,52]. In a singular contradicting report amphibole fibers outnumbered chrysotile ones in anthracotic “black spots” in the parietal pleura sampled during thoracoscopy from all 14 studied individuals [53]. Chrysotile may undergo not only longitudinal splitting but also breakage into shorter fibers, which may be cleared more readily [18]; however, short chrysotile fibers were reported to prevail in the pleura [48,52]. The paradigm of fiber migration to the pleura agrees with the primary affect of asbestos-related Mt usually occurring in the parietal rather than visceral pleura [54].

Statements and conclusions by Bernstein et al. are supported by numerous self-references [41,55]. It has been commented, however, that Bernstein’s experimental findings contradict results obtained by independent researchers and can only be explained by an aggressive pre-treatment of fibers, inducing faults and fragility in the fibers’ structure, leading to their hydration and breaking [56]. Note that decomposition by acids does not necessarily mean easy solubility in living tissues. Different types of fibers were tested for solubility

in the Gamble's solution, which is similar in composition to lung fluid except for organic components [57], and both chrysotile and crocidolite had very low solubility. The dissolution values ranged from a few nanograms of dissolved silicon per square centimeter of fiber surface (chrysotile and crocidolite) to several thousands of ng cm<sup>-2</sup> (glass wools). On the contrary, aramide and carbon fibers were demonstrated to be practically insoluble [57]. It means that certain artificial fibers, proposed as asbestos substitutes, are more biopersistent than asbestos fiber. The study [57] was cited in [55]; but the results were not discussed.

Chrysotile was demonstrated to cause chromosomal aberrations and to induce pre-neoplastic transformations of cells in vitro [58,59]. In certain animal experiments, the amphiboles and chrysotile were shown to be nearly equally carcinogenic for the induction of both Mt [50,58,60,61] and lung cancer [62,63]. Chrysotile was found to be even more carcinogenic than amphiboles in [60], where it was pointed out: "There was no evidence of either less carcinogenicity or less asbestosis in the groups exposed to chrysotile than those exposed to the amphiboles" [60]. Technical details of the study [60] were discussed in [55] but not this essential result. In [64], chrysotile asbestos produced far more lung fibrosis and pulmonary neoplasia than the amphiboles, which was explained by a relatively high fraction of fibers longer than 20 µm in the chrysotile dust used in this experiment [18]. It is known that carcinogenic effect depends on the fiber dimensions (length, diameter) [10,65,66]. A comprehensive review [46], not cited in [41,55], concluded that animal studies indicate an approximately equal risk for all asbestos fibers: "Even if one accepts the argument that chrysotile asbestos does not induce Mt (which we do not), the risk of lung cancer (and asbestosis) cannot be dismissed, and chrysotile appears to be just as potent a lung carcinogen as the other forms of asbestos" [46].

Furthermore, it was commented that "Bernstein and colleagues completely ignored the human lung burden studies that refute their conclusion about the short biopersistence of chrysotile"; more details and references are in [67]. Statistically significant dose-response relationships between the odds ratios for mesothelioma and concentrations of asbestos fibers of different types were reported [68]. In particular, in the group with only chrysotile fiber in the lungs, a statistically significant trend of an increasing relative risk of mesothelioma with increasing fiber content was demonstrated [68]. This paper was not cited in [41,55]. Further reports [69,70] on persistence of chrysotile fibers in the lungs and/or their possible association with Mt and lung cancer, not cited in [41,55], were discussed in [67]. In the author reply [71], the arguments from [67] have not been adequately responded, being dismissed by a declaration that the studies [68,69] "appear to support the concepts put forward by Bernstein et al." followed by self-references [71]. Other reports and reviews [43-48,51,56,58,63,72-75], not supporting the authors' concept, are also not cited in the voluminous reviews [41,55]. Another example: Bernstein et al. cite a rather nondescript phrase from the review "Mesothelioma from chrysotile asbestos" [55,76] that chrysotile is an "exclusive or overwhelming fiber exposure", disregarding the main conclusion: "Chrysotile asbestos, along with all other types of asbestos, has caused mesothelioma" [76]. It was reasonably concluded that by failing to analyze or even mention contradicting data, Bernstein et al. did not provide an

objective analysis, and have created the impression that they have published a document to support the interests of chrysotile producers [56,67]. It should be added that some papers by Bernstein et al. sound remarkably similar to Russian publications obviously promoting chrysotile [39,40].

Association of Mt with crocidolite as opposed to chrysotile was advocated by J. Christopher Wagner, mainly on the basis of epidemiologic data, propagating the difference between white (chrysotile) and blue (crocidolite) asbestos [77], although it was partly at variance with his own experiments [60,61]. Wagner's epidemiological data were from crocidolite-exposed workers, where the relatively large number of registered Mt cases could have been caused by a well-aimed search and higher exposures to asbestos during the 1950s and possibly earlier given long latency period of malignant Mt. The high incidence of Mt in workers exposed to crocidolite could also have been related to a lack of control for potential differences in exposure levels [78]. The screening-effect has probably influenced results also of other studies of amphibole-exposed workers. Reported associations between the Mt incidence and the time of a first exposure, duration of exposure and cumulative exposure [79] can be explained by dose-related differences in medical surveillance and self-reporting, a mechanism discussed in the context of radiation-related conditions [80]. The evidence in favor of crocidolite toxicity based e.g. on the Wittenoom cohort studies seems to be compelling [81-83], although the number of deaths with mesothelioma in men in the period 1987 to 2008 remained similar to the lowest predictions (the number of Mt in the past 8 years was higher than predicted - 74 vs. 63) [83], while genetic predisposition was discussed along with asbestos as an etiologic factor of Mt [84]. There is considerable evidence that the risk of Mt is enhanced after exposure to chrysotile without amphibole admixture [46,48,72-76,85]. There has been also an alternate view [86,87] e.g. that that the exposure-specific risk of Mt from three commercial asbestos types (chrysotile, amosite and crocidolite) is broadly in the ratio 1:100:500 [88]. However, in a later publication by the same authors, the proportion 1:5:10 is discussed; and it is acknowledged that recent evidence had strengthened the case for the proposition that the per-fiber risk of mesothelioma from chrysotile in textile plants is greater than it is in mines [89]. According to [46,62,63], there is no epidemiological or toxicological evidence that chrysotile is less potent than other forms of asbestos for induction of lung cancer, which is essential because of much higher prevalence of lung cancer. It has been suggested that the difference between chrysotile and amphibole fibers for lung cancer is between 1:10 and 1:50 [88]. The same researchers [88] acknowledged that, in view of the evidence that all three asbestos types have produced a similar level of lung tumors in animal inhalation experiments [46], it is problematic to reconcile the animal and human data. The proposed explanation was that "in humans chrysotile (cleared in months) might have less effect than the amphibole fibers (cleared in years)" [88]. It was the purpose of this review to question the latter argument (chrysotile clearance from the lung may be partly explained by fiber splitting and migration to the pleura) and objectivity of human studies in general (unsharp delineation of Mt as an entity, screening effect). Moreover, the current Mt- and asbestos-related research is not free from bias. This is, predominately due to industrial interests, particularly the promotion of chrysotile interfering with objectivity in some studies



[90]. The quality of research and reviewing should be taken into account defining inclusion criteria for studies into meta-analyses and systematic reviews. It seems that some voluminous papers are contributing more to the tangling than to clarifying the problem. A possible solution could be large-scale chronic bioassays including larger animals and primates [91]. Among others, such experiments may help to identify an actual “no-effect” or threshold exposure levels for different fibers. The bioassays with fiber inhalation, comparable to exposures in the asbestos industry, can be organized e.g. in stray animal shelters and breeding facilities for primates without application of invasive methods. Sine qua non conditions of animal experimentation must be objectivity and integrity.

The conclusion of the WHO and IARC assessments is that chrysotile causes cancer of the lung, mesothelioma and asbestosis [85]. Different asbestos types can be mixed in the international trade [92]. As mentioned above, carcinogenic effect depends not only on biopersistence but also on fiber dimensions notwithstanding fiber type [10,65,66,93], which is an additional argument in favor of the a priori “all fibers equal” approach to different types of asbestos and its substitutes. Admittedly, it is possible that the difference in toxicity between the amphiboles and chrysotile is so considerable that it must be reflected in regulations. In the author’s opinion, the “all fibers equal” basis of official regulations can be accepted provisionally, pending objective and reliable evidence. It would be not only a technically most plausible solution, but also partly compatible with current, albeit conflicting, knowledge. Considering the strong economic interests behind the research comparing toxicity of different asbestos types [94], any deviations from the “all fibers equal” [95] concept must be based on high-quality, independent research.

## Conclusion

Current asbestos-related regulations are irrational. Asbestos production and trade is prohibited in some countries, while others have maintained or increased production and use in recent years. Substitution of asbestos by artificial fibers would not necessarily lower or eliminate health risks [10-13,96,97]. The increased incidence of malignant Mt in developed nations [98,99], despite the prohibition of asbestos, is probably at least in part due to improved diagnostics, an increasing awareness of Mt, a screening effect in asbestos-exposed populations, and some over-diagnosis in conditions with an unclear demarcation of malignant Mt as an entity. This screening effect has probably contributed to an increased registered incidence of all asbestos-related diseases in exposed populations, and a resultant over-estimation of dose-response relationships particularly after low-dose exposures. On the basis of independent scientific data, the bans and restrictions on asbestos in some countries should therefore be re-examined and potentially revised. Any permit of continued production or use of asbestos materials must be accompanied by regulations and efficient measures to prevent environmental contamination, domestic or passive exposures, associated even with minimal additional risk.

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