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Exaggerated Risk Perception of Low-Dose Exposures to Asbestos: Cui Bono?

Keywords: Asbestos; Chrysotile; Mesothelioma; Lung cancer

Abstract

Asbestos is a known carcinogen. Asbestos-related risks have been estimated on the basis of data from the past, when professional exposures were higher than today. Fibres are present in the environment due to erosion of surface deposits and human activities unrelated to asbestos industry. If searched for, asbestos fibres are often found post mortem. Bias can be encountered in asbestos research e.g. attributing of mesothelioma or lung cancer to asbestos if fibres are found, although cause-effect relationships remain unproven. Some studies rely on work or residence histories of questionable reliability. It can be reasonably assumed that the non-use of asbestos-containing brakes, fireproofing and insulation has increased the damage and numbers of victims of traffic accidents, fires and armed conflicts. Today, when a probability of conflicts seems to be enhanced, the attitude to asbestos should be changed. Asbestos is banned in some countries, while others continue production and exports. Some anti-asbestos activists have apparently served certain governments or companies. The same is partly true for the anti-nuclear activism. Different asbestos types have their technical advantages and preferred application areas. Reliable information about toxicity of fibres can be obtained in lifelong bioassays.

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Introduction

Asbestos is a proven carcinogen. Health risks from asbestos have been evaluated on the basis of data from the past, when workers' exposures were higher than today. The linear no-threshold model has been applied to asbestos-related risks although its applicability is unproven and remains arguable both for pleural and lung tumors [1-3]. There is an opinion that a large part of asbestos exposure in developed countries ended ~40 years ago and that exposures from new asbestos-containing products are insignificant [3]. Asbestos fibres are present in the natural environment due to erosion of surface deposits. Naturally occurring asbestos has been commonly found in populated areas [4]. The natural emission contributes to a dispersion of chrysotile and amphibole asbestos fibres. Presumably, natural releases dwarf anthropogenic contributions to the atmospheric dispersion of the above-named fibres [4,5]. Air, soil and water may be contaminated by asbestos and other potentially harmful fibres due to human activities unrelated to asbestos e.g. land excavation, slopes reprofiling and tunneling [6,7]. In one study, asbestos fibres were found in 35 of 55 (63.6%) autopsy cases from the general population [8]. At autopsies of exposed people, pulmonary and pleural tissues are sampled more abundantly and examined more thoroughly, hence the higher probability to find fibres and to diagnose pathological conditions. The presence of fibres by itself proves neither professional exposure nor asbestos-related disease. Inhalation and discharge of fibres are in a dynamic balance [8,9]. By analogy with other substances in the natural environment, it can be assumed that there is a harmless (threshold) fibre concentration in the ambient air. The concept "one fibre can kill" may have as little relevance to reality as it is for environmental levels of numerous substances and physical factors that are toxic at higher doses. The screening has obviously contributed to the enhanced detection rate of mesothelioma and lung cancer in asbestos-exposed populations. Bias is not infrequent in asbestos research, e.g. attributing to asbestos of malignancies in the presence of fibres, although a cause-effect relationship remains unproven. Some studies rely on work or residence histories and interviews with relatives of questionable reliability [10].

Malignant pleural mesothelioma (MPM)

The unchanging or increasing incidence of MPM in the countries applying asbestos bans is caused, at least in part, by the growing public awareness, improvement of diagnostics, screening effect in exposed populations and some overdiagnosis in view of the unclear demarcation of MPM as an entity. Apart from asbestos, potential etiologic factors of MPM include various mineral and artificial fibres, virus SV40, ionizing radiation, chronic inflammation (empyema, tuberculosis) and genetic predisposition [11-16]. For example, erionite is regarded to be a more potent carcinogen than asbestos. Human activities result in dispersal of erionite and other potentially carcinogenic fibres into populated areas [6,11]. Certain types of carbon nanotubes have been classified as possible human carcinogens [17].

Furthermore, there are indications that the virus SV40 has contributed to the worldwide incidence increase of mesothelioma in recent decades. The incidence increase of MPM in the 1960s coincided with human exposure to the virus in the period 1955-1963 (and later in some countries) when poliovaccines were contaminated with viable SV40 [18,19]. The virus continues circulating independently from contaminated vaccines [19-21]. SV40-like DNA sequences and viral oncoprotein were found in MPMs of different histological types while some investigators reported negative data; reviewed in [19,20]. Antibodies against SV40 were detected in sera of MPM patients in 34% vs. 20% in healthy subjects (odds ratio 2.049, CI 95% 1.32-3.22). These results indicate that SV40 is linked to a large fraction of MPM and also that the virus circulates in human population [20]. After a laser microdissection, SV40 was demonstrated in MPM cells but not in nearby stromal cells [18]. SV40 is oncogenic in experimental animals [21]. When it was injected via the intracardiac or intraperitoneal routes, ≥50% of hamsters developed mesothelial tumors; 100% of hamsters injected into the pleural space developed mesotheliomas

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[22]. Systemic injections caused mesothelioma in ~60% of hamsters [11]. It can be assumed that invasive manipulations e.g. bronchoscopy used with above-average frequency in people exposed to asbestos contributed to dissemination of SV40, resulting in additional MPM cases. In the former Soviet Union (SU), bronchoscopy and bronchial biopsy were recommended and performed in patients with asbestos-related bronchitis [23,24]. Due to the ageing population and because some people are predisposed to MPM, given various mutations and carcinogens, the majority of mesotheliomas in future are expected to be unrelated to asbestos [3].

MPM is not clearly demarcated from other cancers. Histologically, MPM can resemble different cancers while the lack of specific biomarkers makes the diagnosis difficult. Tumors can undergo de-differentiation, becoming histologically similar to MPM. The differential diagnosis varies depending on the MPM subtype. Spindle cell tumors of pleura are especially difficult to diagnose while immunohistochemistry is of limited help [15,25]. The differential diagnosis of MPM is a known problem; revisions of histological archives regularly found misclassified cases [25,26]. In one study, the initial diagnosis was confirmed in 67% of cases, ruled out in 13%, and remained uncertain in the rest [27]. Another expert panel changed the diagnosis in 14% of 5258 mesotheliomas [11]. According to an estimate, ~10% of MPMs in the United States were misdiagnosed [26]. Among reasons of the diagnostic uncertainty is an unclear demarcation of MPM from other cancers and insufficient experience due to the rarity of MPM [25,26]. On the contrary to the general population, in asbestos-exposed people the well-aimed search for MPM is performed by experts. Accordingly, more MPMs are found, questionable or borderline cases being sometimes classified as MPM. Litigation might also contribute to misattribution of cases to asbestos [10].

The lack of reliable biomarkers makes the diagnosis of MPM challenging [18]. Mesothelin has been discussed as one of the most promising markers. However, it is not sufficiently sensitive, being overexpressed in different cancers [11,12,28-30]. On the other hand, mesothelin it is often negative in sarcomatoid and epithelioid MPMs [25]. Osteopontin has been a promising marker but the data are inconsistent. Similar to mesothelin, the clinical utility of osteopontin and fibulin-3 is limited due to low sensitivity [30]. The microRNA down-regulation in MPM compared to lung cancer was regarded to be a promising marker; but diagnostic accuracy is moderate as microRNAs are deregulated also in some other malignancies [31,32]. Chromosomal aberrations in MPM are heterogenous [16,33]. The information on the molecular basis of MPM is insufficient [34]. According to the Helsinki Criteria, established for attribution of mesothelioma to asbestos, no specific recommendations can be given for the use of markers in the screening for MPM [35,36]. Moreover, MPM may exhibit various molecular setups in different areas i.e. intra-tumoral heterogeneity and subclonality [37]. Contrary to other malignancies, driver mutations have not been clearly determined in MPM. There are no strong genetic markers [38,39]. Diagnosis of MPM on cytomorphological grounds is challenging, especially when reactive atypical mesothelial cells are present. Notwithstanding the plethora of markers, none has been sufficiently specific [36,40]. A tumor diagnosed as MPM using algorithms and panels is not always biologically different from other cancers. The above explains enhanced yield of the screening in exposed populations.

Russian science on asbestos

Asbestos-related diseases have been extensively studied in the former SU. The prevailing opinion has been that, if necessary precautions are taken, modern technologies of asbestos production and processing are safe, while bans applied in some countries are excessive. Health hazards from low fibre concentrations are unproven. No enhanced risks have been demonstrated in residents near modern asbestos-processing plants. Epidemiological studies indicate a threshold [41,42]. Genetic adaptation to a certain level of asbestos fibre inhalation is deemed possible [43]. In the former SU, corrugated asbestos sheets have been broadly used for roofing. The fibre emission from roofing materials during construction and use of buildings is negligible. Fibre concentrations in the indoor air are an order of magnitude below the permissible level [44]. Asbestos-cement pipes have been broadly used for drinking water distribution and deemed safe as no risks from oral intake of fibres have been proven, the more so as fibres are modified by aggregation with cement [45]. Studies show that the use of asbestos-cement pipes does not impair the quality of drinking water and their use has been approved by the Ministry of Health [46]. Asbestos-containing broken-stone ballast – a by-product of chrysotile enrichment - has been used for the gravelling of railroad embankments while enhanced concentration of airborne fibres was noticed both in trains and in nearby townships [47]. Similarly to asbestos-cement, carcinogenicity of fibres in asbestos board is decreased due to aggregation with cellulose. There is no considerable air pollution by fibres from car brakes, while the traffic is safer with asbestos-containing linings [48,49]. In the process of braking, asbestos is transformed to forsterite that is practically harmless [50,51]. Asbestos-containing materials (flat sheets, millboard, paper, clothing, gaskets, etc.) are broadly used now as before. Installation and repair without processing of asbestos-containing parts is deemed safe [49]. No increase in the registered incidence of mesothelioma has been found either among asbestos workers or residents of the areas with modern asbestos industry [52]. It was concluded on the basis of 3576 MPM cases that asbestos is neither a leading nor obligate causative factor [53].

Asbestos produced in Russia is almost exclusively chrysotile; it is broadly used and exported to the countries where it is not banned [54]. The low toxicity of chrysotile compared to amphiboles is often stressed in the Russian literature e.g. “Chrysotile fibres are easily dissolved and discharged” [55]. The author does not intend to say that papers biased in favor of chrysitile come only from Russia. Chrysotile was produced also in other countries, for example Canada and Italy; some papers of questionable objectivity are discussed below. However, in both latter countries asbestos is banned, whereas Russia continues production and exports. The message of this article is that the non-use of asbestos-containing brakes, fireproofing and insulation probably has augmented the damage and numbers of victims of traffic accidents, fires, terrorist attacks and international conflicts. Today, as the probability of armed conflicts seems to be enhanced, the attitude to asbestos should be changed. Most importantly, asbestos-related research must be separated from economical and political interests. Some Russian experts admitted that the concept of much higher toxicity of inhaled amphibole fibres compared to chrysotile has not been sufficiently founded [56]. Carcino-, fibro-, mutagenicity and cytotoxicity of chrysotile was confirmed both in experiments and

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epidemiological studies [57]. In some experiments, carcinogenicity of chrysotile did not differ significantly from that of amphiboles [58].

Chrysotile vs. amphiboles

Numerous studies indicated that serpentine (chrysotile) is less toxic than amphibole (actinolite, amosite, anthophyllite, crocidolite, tremolite) asbestos but there are discrepancies between human (epidemiological) and experimental data. All asbestos-related diseases have been found in workers exposed to chrysotile [59]. As mentioned above, there is a strong economic interest to support chrysotile in Russia and some other countries. The differences in toxicity must be tested and quantified by research independent of industrial interests. Statements by the leading Russian expert Nikolai Izmerov (1927-2016) that chrysotile is "easily dissolved and discharged" [55] and those by David Bernstein "Chrysotile fibres are rapidly cleared from the lung in marked contrast to amphibole fibres which persist" [60] sound similarly. Moreover: "Following short-term exposure the longer chrysotile fibres 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" [61]. Given the possibility of a post-depositional translocation of chrysotile fibres from the lung to pleura [62-66], the rate of asbestos retention cannot be determined only by evaluation of fibre contents in pulmonary tissues. In accordance with the concept of fibre migration to the pleura, primary foci of asbestos-related mesothelioma are more often located in the parietal rather than visceral pleura [67]. Conclusions by Bernstein et al. about low biopersistence of chrysotile were supported by self-references [61,68]. However, results of their experiments can be explained by a chemical pre-treatment of fibres, inducing hydration, fragility and breaking [69]. "Bernstein's study protocol induces a very short fibre half-life, from which he concludes weak chrysotile carcinogenicity. Bernstein's findings contradict results obtained by independent scientists. Bernstein's results can only be explained by an aggressive pre-treatment of fibres, inducing many faults and fragility in the fibres' structure, leading to rapid hydration and breaking of long fibres in the lungs" [69]. The decomposition by acids does not prove solubility in living tissues. The dissolution at neutral and acid (~4.5) pH is often incongruent [70]. In leaching tests using acid (pH = 4) "artificial lysosomal fluid" (ALF), the dissolution rate of chrysotile was indeed faster than that of amphiboles [54]. The pH value of ALF is usually ~4.5 [71,72]. In the study [73], various fibres were tested in the Gamble's solution imitating pulmonary interstitial fluid. This solution is a mixture of salts with pH ~7.4 [71,72]. Both chrysotile and crocidolite manifested very low solubility in the Gamble's solution [73]. The dissolution ranged from a few nanograms of dissolved silicon per cm^2 of fibre surface (chrysotile and crocidolite) to several thousand ng/cm^2 (glass wool). Aramide and carbon fibres were practically insoluble [73]. The latter study was referenced but not discussed by Bernstein et al. [68].

The accelerated clearance of chrysotile from the lung can be partly attributed to the longitudinal splitting of fibres into thin fibrils that can evade detection. As a result, the total number of fibrils would increase possibly together with the carcinogenic potency [62,64,66,74-76]. Presumably, the thinner a fibre, the higher would be its carcinogenicity, as it can penetrate tissues more efficiently [77]. Asbestos fibres are found in the pleura post mortem, chrysotile being the predominant fibre in pleural plaques and pleural tissues in general [63,65,78,79]. The concept of fibre migration to the pleura agrees with the fact that a primary tumor of asbestos-related mesothelioma is more often located in the parietal rather than visceral pleura [67]. Moreover, "Bernstein and colleagues completely ignored the human lung burden studies that refute their conclusion about the short biopersistence of chrysotile" [80]. Numerous relevant publications, unsupportive of Bernstein's conclusions, were not cited in his reviews; more details and references are in [2]. 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 impression that they published a document to support the interests of chrysotile producers [69,80].

The incidence of mesothelioma is enhanced after exposures to pure chrysotile [59,81]. The relatively high frequency of mesothelioma among workers having contact with amphiboles was explained by averagely higher exposures [82]. As mentioned above, there are discrepancies between animal and human data. The evidence for a difference in the potency between chrysotile and amphiboles in inducting lung cancer is "weak at best" [83]. In certain animal experiments, the carcinogenic potency of amphiboles and chrysotile was found to be nearly equal for induction of both mesothelioma and lung cancer [75,84-88]. Chrysotile was even more carcinogenic than amphiboles in a study, whereas 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" [86]. Technical details of the latter study were discussed by Bernstein et al. [68] but not this conclusion. In one rat study, chrysotile induced more lung tumors and fibrosis than amphiboles, which was explained by a large fraction of fibres longer than 20 μm in the used chrysotile preparation [89]. Chrysotile induced chromosomal aberrations and pre-neoplastic transformations of cells in vitro [84,90].

In humans, the lung cancer risk difference between chrysotile vs. amosite and crocidolite was estimated in the range 1:10 to 1:50. The risk ratio of mesothelioma was estimated, respectively, as 1:100:500 [1], cited in reviews [27,91]. In a later publication, another ratio (1:5:10) was suggested [92]. The same researchers noticed that, in view of the fact that different asbestos types produced a similar harvest of lung tumors in animal experiments, it is problematic to reconcile animal and human data. The proposed explanation was that "in humans chrysotile (cleared in months) might have less effect than the amphibole fibres (cleared in years)" [1]. However, there are no reasons to suppose substantial interspecies differences in the fibre clearance. As mentioned above, chrysotile clearance from the lung may partly result from the fibre splitting and movement to the pleura. As for epidemiological studies, some of them are biased due to the screening effect with over diagnosis in exposed populations, unclear demarcation of MPM from other cancers, imprecise exposure histories and, last but not least, conflict of interest in researchers associated with the chrysotile industry.

The toxicity of fibres is generally determined by the three "D's": dose, dimension and durability (biopersistence). The biopersistence being equal, differences in carcinogenicity are associated with the length and thickness of fibres [93]. Long fibres of chrysotile were found to possess a relatively high toxicity as they cannot be efficiently engulfed and cleared by macrophages [94,95]. Agglomeration of

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long chrysotile fibres induces high biological response in terms of "frustrated phagocytosis" [54]. According to another report, thin short chrysotile fibres were found to be prevailing in the lung and pleura of patients with MPM [96]. In addition, tremolite admixture in chrysotile products can potentiate carcinogenicity [97]. A review concluded that there is no evidence that increased incidence of MPM in chrysotile workers was caused solely by tremolite [65]. In one epidemiological study, the difference in MPM risk from pure chrysotile and its mixtures with amphiboles was insignificant [98]. The question of relative potency of different asbestos types was examined in a meta-analysis of 19 epidemiological studies assessing the influence of research quality on exposure-response estimates for lung cancer. The difference between chrysotile and amphiboles was difficult to ascertain when the meta-analysis was restricted to studies with fewer exposure assessment limitations i.e. of higher quality [91]. After accounting for quality, there appeared to be little difference in the dose-response slopes for cumulative exposure to chrysotile compared to amphiboles [91,99]. According to a systematic review, pooled risk estimates for lung cancer were higher after exposures to amphiboles - 1.74 (95% CI 1.18 to 2.57) than to chrysotile - 0.99 (95% CI 0.78 to 1.25); but the overall risk tended to be higher in intermediate- rather than in high-quality studies (there was no poor-quality group): 1.86 (95% CI 1.27 to 2.72) vs. 1.21 (95% CI 0.79 to 1.87) [100]. Significant differences between results obtained in high- vs. low-quality studies are indicative of bias due to a conflict of interest, as it is obviously easier to find support for preconceived ideas in the domain of poor-quality and manipulated studies rather than in high-quality research. The difference in toxicity between chrysotile, amphiboles and other fibres should be evaluated by research independent of industrial interests.

Discussion & Conclusion

The screening effect and increased attention of exposed individuals to their own health will probably result in new reports on increased cancer and other health risks. This would further contribute to the overestimation of risks from low-dose exposures. A possible way to objective information about toxicity of different fibre types could be lifelong bioassays using not only rodents but also larger animals including primates [101]. The bioassays with fibre inhalation, comparable to exposures in the asbestos industry, can be performed without invasive procedures thus being ethically acceptable. Animal experiments using "exposure concentrations that were orders of magnitude greater than those reported for worker exposure" [102] are of limited informativity. A substitution of asbestos by artificial fibres would not necessarily eliminate health risks [13,14,17]. The carcinogenicity of asbestos substitutes e.g. carbon nanotubes comes to light these days. Studies indicate that asbestos fibres and carbon nanotubes with certain dimensions exert toxic effects through similar mechanisms such as macrophage activation resulting in inflammation [103]. As mentioned above, carbon nanotubes are biopersistent, certain varieties being classified as possible human carcinogens [17].

The number of publications about asbestos is growing; it is difficult to distinguish between objective and biased information. Many papers are biased in favor of chrysotile vs. amphibole asbestos. Internationally traded chrysotile products e.g. from China contain admixtures of amphiboles [104]. Different asbestos types have their technical advantages. Amphiboles (crocidolite, anthophyllite and others) are acid-resistant, thermo-stabile and durable [105]. Asbestos is a low-cost material and an excellent reinforcing fibre. The traffic is safer with asbestos-containing linings. Asbestos cement (fibrolite) constructions are sturdy and inexpensive; their extensive use started during the World War II. The fireproofing properties of asbestos are well known. It can be reasonably assumed that the non-use of asbestos-containing brakes, fireproofing and insulation laggings has augmented the numbers of victims of traffic accidents, fires and armed conflicts. Nowadays, when a probability of conflicts seems to be enhanced, the attitude to asbestos should be changed. Most importantly, asbestos-related science must be separated from industrial interests. Asbestos bans have been partly based on the research influenced by industrial and political interests. Some anti-asbestos activists may have conflicts of interest related to the manufacturing of chrysotile or asbestos substitutes, lawyers' earnings from litigation, or interests of construction firms performing asbestos removal with exposures of abatement workers. It was noticed that "grassroots intimidated governments into approving more restrictive regulations" [106]. Apparently, some anti-asbestos activists served certain companies or governments. Asbestos is banned in some countries, while others are increasing production and exports. The same considerations pertain also to the anti-nuclear activism and Green movement in general. In view of the growing international tensions, their unconstructive and defeatist role is becoming obvious. Psychological mechanisms seem to be exploited: repression (Verdrängung) of real dangers and redirection of public anxiety and protests against surrogate targets. Cui bono? Citizens should be aware that their best intentions may be misused to disadvantage their own countries.

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