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Asbestos-Related Cancer: An Update

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Abstract

Asbestos-related risks have been estimated on the basis of data from the past, when professional exposures were higher. Fibers are present in the environment due to erosion of surface deposits and human activities unrelated to asbestos industry. If searched for, asbestos fibers are frequently found at autopsies. Bias can be encountered e.g., attributing of mesothelioma and lung cancer to asbestos when fibers are found, although cause-effect relationships remain unproven. A history of exposure per se is not a proof of causation. Some studies rely on work or residence histories of questionable reliability. Asbestos is a low-cost material and an excellent reinforcing fiber. Different asbestos types have their technical advantages and preferred application areas. The road traffic is safer with asbestos-containing brake linings. Asbestos cement constructions are sturdy and inexpensive; its fireproofing properties are well known. It can be reasonably assumed that the non-use of asbestos would weaken defenses of civilized countries, enhance the damage from fires and armed conflicts. Apparently, some scientific writers and environmental campaigners act in accordance with the interests of foreign governments. Today, when a probability of conflicts is enhanced, the attitude to asbestos should be changed. The research must be separated from economical and political interests. Reliable information can be obtained in lifelong bioassays.

Introduction

It is important in our time of international tensions that scientists preserve objectivity. Potential conflicts of interest should be discussed. There have been endeavors to demonstrate that certain environmental campaigners act in accordance with the interests of companies and governments selling petroleum and natural gas [1]. Apparently, the same tendency exists for chrysotile asbestos [2]. It is known that exposure to asbestos can cause diseases of lungs and pleura: mesothelioma, lung cancer (LC), asbestosis, pleural plaques and others. Malignant pleural mesothelioma (MPM) is a rare tumor; asbestos is widely believed to be its leading cause. According to a recent estimate, asbestos causes about 255,000 deaths worldwide yearly, of which professional exposures are responsible for approximately 233,000 [3]. There are, however, reservations. Health risks were extrapolated from the mid 20th century, when fiber concentrations in the industry were higher than today. The linear no-threshold model was used for the risk estimation, although its relevance is unproven [4]. Dangerous exposures have largely ended in developed countries for 40-50 years. The vast majority of mesotheliomas are expected to be unrelated to asbestos by the year 2035 [4].

Both chrysotile and amphibole asbestos get into the environment due to erosion of natural deposits, outnumbering anthropogenic fibers in many places [5,6]. Air, soils and waters are often contaminated by fibers due to industries unrelated to asbestos, land excavation, slopes reprofiling, tunneling etc. Naturally occurring asbestos has been commonly found in populated areas [5]. Natural releases dwarf anthropogenic contributions to the atmospheric dispersion of the fibers in some places [5,6]. In one study, asbestos fibers were found in 35 of 55 (63.6%) autopsy cases from the general population [7]. At necropsies of people from risk groups, lungs and pleura are abundantly sampled and thoroughly examined. The detection of fibers proves neither industry-related exposure nor asbestos-caused disease [7,8]. Some studies rely on work or residence histories and interviews of questionable reliability [9]. Inhalation and discharge of fibers occur normally being in a dynamic balance [7,8]. By analogy with other environmental factors, the existence of a harmless (threshold) fiber concentration in the ambient air can be reasonably assumed. The concept that "one fiber can kill" has as little relevance as it is for environmental levels of numerous substances and physical factors that would be harmful at higher doses. The screening has contributed to enhanced detection rates of mesothelioma and LC in asbestos-exposed populations [9]. Bias is not infrequent in asbestos research, e.g., attributing to asbestos of mesothelioma or LC in the presence of fibers, although causality remains unproven. According to the Helsinki Criteria for diagnosis of asbestos-related diseases, "even a brief or low-level exposure should be considered sufficient for mesothelioma to be designated as occupationally related" [10]. This concept has been criticized because it may lead to misclassification of spontaneous cases as occupational ones [11]. In regard to LC, the Criteria leave space for subjectivity: "Cumulative exposure, on a probability basis, should thus be considered the main criterion for the attribution of a substantial contribution by asbestos to LC risk" [10].

Asbestos and Mesothelioma

The asbestos ban is currently applied in 55 countries at least [12]. The largely stable incidence of mesothelioma in industrialized countries despite the bans for over 20 years is partly caused by increasing awareness, improvements of diagnostic equipment, screening in the risk groups, and some percentage of overdiagnosis because of the imprecise demarcation of MPM from other cancers. Among causative factors are various fibers (erionite, carbon nanotubes, metal nanowires), radiation, simian virus 40 (SV40) and inflammatory conditions such as empyema and tuberculosis [13,14]. Erionite is believed to be a more potent carcinogen than asbestos. Human activities result in dispersal of erionite and other potentially carcinogenic fibers into populated areas [15,16]. Certain types of carbon nanotubes have been classified as possible human carcinogens [17]. For example, intratracheal administration of multi-walled carbon nanotubes-7 produced malignant mesothelioma in rats more

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frequently than crocidolite [18,19]. Furthermore, there are indications that virus SV40 has contributed to the worldwide incidence increase of mesothelioma in recent decades despite asbestos bans [20]. SV40-like DNA sequences have been regularly found in MPMs [21]. After a laser microdissection, SV40 was demonstrated in MPM cells but not in nearby stromal cells [20]. The quantity of reports on SV40 DNA sequences in mesotheliomas outnumbered that regarding other tumors [22]. SV40 can replicate in human mesothelial cells that remain infected for a long time releasing viral progeny. When SV40 was injected via the intracardiac or intraperitoneal routes, ≥50% of hamsters developed mesothelial tumors; 100% of hamsters injected into the pleural space developed mesotheliomas [23]. Systemic injections caused mesothelioma in ~60% of hamsters [16]. An incidence increase of MPM was recorded after the human exposure to SV40 in 1955-1963 (and later is some countries) when polio vaccines were contaminated with viable SV40 [20]. It can be reasonably assumed that bronchoscopy and other invasive manipulations, applied above-average in people exposed to asbestos, contributed to dissemination of SV40 and other viruses. Bronchoscopy and bronchial biopsy were performed and recommended in Russia for patients with asbestos-related bronchitis [24,25]; more details are in [26]. The bronchoscopy was used in patients with suspected dust diseases, pneumonia and other conditions, sometimes with questionable indications [24-28]. Finally, the genetic predisposition plays a role in the etiology of MPM [13]. Given the presence of various mutations and carcinogens, the majority of mesotheliomas in future are expected to be unrelated to asbestos [4].

MPM had no diagnostic category within the International Classification of Diseases (ICD) till the 10th Edition [29]. Histologically, MPM can resemble different cancers while the lack of specific markers makes the diagnosis difficult. Other malignancies can undergo de-differentiation, becoming histologically similar to MPM. The differential diagnosis varies depending on the MPM subtype. Spindle cell tumors of pleura are particularly difficult to diagnose while immunohistochemistry is of limited help [30-32]. Revisions of histological archives regularly found misclassified cases [32,33]. The absence of pathognomonic markers makes the differential diagnosis difficult, especially that of sarcomatoid MPM [34]. Immunochemical methods are not always helpful. Reportedly, around 1/10 of malignant mesotheliomas in the United States have been misdiagnosed [33]. After a re-examination, the initial histopathological diagnosis of MPM remained unchanged in 67% of cases, was ruled out in 13% and left uncertain in the others [35].

The molecular basis of mesothelioma is largely unclear [36]. From numerous markers, no one is sufficiently specific. Mesothelin has been encouraging although it is overexpressed in different cancers [37]. According to a meta-analysis, fibulin-3 had the highest diagnostic value for MPM [38], but it is also overexpressed in other cancers. A comparative analysis has suggested that fibulin-3 correlates less accurately than mesothelin with PM diagnosis [37]. Osteopontin has been promising but results are inconsistent [34]. The diagnostic value of the altered microRNA expression was limited [39,40]. There are many markers with modest diagnostic accuracy [37,40]. Chromosomal aberrations in malignant mesothelioma are varied. The cytological diagnosis is known to be difficult. The Helsinki Criteria made no specific recommendations regarding biomarkers for the diagnostics of mesothelioma [10].

MPM often exhibits intra-tumoral heterogeneity and subclones [41]. Unlike many cancers, driver mutations have not been firmly established [42]. The sensitivity of closed pleural biopsies and fluid cytology is low [43]. A neoplasm classified as mesothelioma using available methods and marker combinations is not necessarily different from other tumors. The imprecise demarcation of MPM from other malignancies enhances the screening effect and diagnostic yield in exposed populations thus contributing to an overestimation of the asbestos-related risks. In populations exposed to asbestos, experts specifically search for MPM. As a result, MPMs are detected above average while overdiagnosis in questionable and borderline cases may occur. Conversely, in the general population MPM is sometimes missed and diagnosed as other cancers [38]. A tumor diagnosed as MPM using algorithms and panels is not necessarily different from other malignancies.

Russian Science on Asbestos

Asbestos produced in Russia is predominantly chrysotile, low carcinogenicity of which is often stressed. It was claimed without references that chrysotile fibers are easily dissolved in biological fluids and quickly removed from the lungs [44]. At the same time, the carcino-, fibro- and mutagenicity of chrysotile has been confirmed both in experimental and in human research [45-49]. The consensus in the Russian literature is that modern asbestos industry is acceptably safe if precautionary measures are taken; while bans applied in other countries are excessive. Health hazards from low fiber concentrations are unproven. No enhanced risks have been demonstrated in residents near modern asbestos-processing facilities. Malignancies related and unrelated to asbestos are indistinguishable from each other. Epidemiological studies indicated a threshold [50,51]. Genetic adaptation to a certain level of fiber inhalation was regarded to be possible [52]. In the former SU, corrugated asbestos sheets have been broadly used for roofing. The fiber emission from roofing materials during construction and use of buildings is believed to be negligible. Fiber concentrations in the indoor air are an order of magnitude below the permissible level [53]. Asbestos-cement pipes are used for drinking water regarded to be safe as no risks from oral intake of fibers have been proven, the more so as the fibers are aggregated with cement. The research demonstrated that asbestos-cement pipes do not affect the quality of drinking water; and their use has been approved by the Health Ministry [54]. Asbestos-containing broken stone, the by-product of chrysotile production, has been used for railroad embankments while increased concentrations of airborne fibers were recorded both in nearby villages and in trains [55]. Similarly, to asbestos-cement, the harm from fibers in asbestos board is decreased because of the aggregation with cellulose. There is no appreciable air pollution from car brakes, while the traffic is safer with asbestos-containing linings. In the process of braking, asbestos is transformed to forsterite, which is practically harmless. 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 believed to be safe [56]. No increase in the detection rate of mesothelioma has been found in workers and residents of the areas around modern asbestos industry facilities [57]. It was concluded on the basis of 3576 MPM cases that asbestos is neither a leading nor obligate etiological factor [58]. However, the most recent study did confirm an increased risk of

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mesothelioma and LC among chrysotile miners and millers [49]. To the best of our knowledge, this is the first large-scale epidemiological study from Russia reporting asbestos-related morbidity and mortality in the modern industry. A similar metamorphosis from absent to significant risk occurred around 2005 in the research about radioactive contaminations and professional exposures in the Urals. An unofficial directive was apparently behind this ideological shift. For ionizing radiation, potential motives of the risk exaggeration were the international help after the Chernobyl accident, publication pressure, stirring anti-nuclear protests in other countries and strangulation of nuclear energy for the boosting of fossil fuel prices [1]. As for asbestos, the probable motive has been supported of anti-asbestos protests. The non-use of asbestos would enhance vulnerability of developed countries, increase the damage from terrorist attacks, fires and armed conflicts.

Serpentine and Amphibole Asbestos

It is widely believed that serpentine (chrysotile) is less toxic than amphibole (actinolite, amosite, anthophyllite, crocidolite, tremolite) asbestos. Chrysotile is predominantly produced in Russia. The low toxicity of chrysotile compared to amphiboles is often stressed. However, some experts admitted that the concept of much higher toxicity of inhaled amphiboles has not been demonstrated satisfactorily. Carcino-, fibro-, mutagenicity and cytotoxicity of chrysotile was confirmed both in experiments and in epidemiological studies performed in Russia [45-47]. In experiments, chrysotile was reported to possess acute toxicity, inducing the granulomatous tissue reaction [48]; its carcinogenicity did not differ significantly from that of amphiboles [59].

Papers by David Bernstein and co-workers [60,61] sound similar to Russian publications cited above, for example: "Following short-term exposure the longer chrysotile fibers rapidly clear from the lung and are not observed in the pleural cavity" [60]. Given the possibility of a post-depositional translocation of chrysotile fibers from the lung to pleura [62-66], the rate of asbestos retention cannot be determined only by fiber counting in pulmonary tissues. Conclusions by Bernstein et al. [60,67] about the low biopersistence of chrysotile were supported by self-references. However, results of their experiments can be explained by a chemical pre-treatment of fibers, inducing hydration, fragility and breaking [68]. "Bernstein's study protocol induces a very short fiber 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 fibers, inducing many faults and fragility in the fibers' structure, leading to rapid hydration and breaking of long fibers in the lungs" [68]. The decomposition by acids does not prove solubility in living tissues. Admittedly, the dissolution of chrysotile may be more efficient in the acidic contents of lysosomes. Different types of fibers were tested in the Gamble's solution imitating pulmonary interstitial fluid: both chrysotile and crocidolite exhibited very low solubility [69]. The dissolution ranged from a few nanograms of dissolved silicon per cm^2 of fiber surface (chrysotile and crocidolite) to several thousands of ng/cm^2 (glass wool). Aramide and carbon fibers were practically insoluble. The study [69] was referenced but not discussed by Bernstein et al. [67]. Only a very small amounts of silicon are dissolved from chrysotile but larger amounts of magnesium [69]. Silicon is mainly responsible for the fiber strength; but washing out of magnesium from fiber surfaces might contribute to the longitudinal splitting. The accelerated clearance of chrysotile from the lung can be partly attributed to the longitudinal splitting into thinner fibers, some of them evading detection. As a result, the total number of fibers would increase possibly together with the caused damage [63-65,70-75]; more references are in [2]. Presumably, the thinner a fiber (within some limits), the higher would-be carcinogenicity, as it can penetrate tissues more efficiently [75]. Chrysotile is a predominant fiber post mortem in the pleura including plaques [66,76,77]. The concept of fiber migration to the pleura agrees with the fact that the primary affect of asbestos-related mesothelioma is usually in the parietal rather than visceral pleura [78].

The incidence of mesothelioma is enhanced after exposures to pure chrysotile [79,80]. The relatively high frequency of mesothelioma among workers after contact with amphiboles was explained by averagely higher exposures [81]. There are discrepancies between animal and human data. The evidence for a difference in potency for LC induction between chrysotile and amphiboles was designated as "weak at best" [82]. In certain animal experiments, the carcinogenic potency of amphiboles and chrysotile was nearly equal both for mesothelioma [70,83-85] and LC [86,87]. Based on rat inhalation studies, the well-known expert J. Christopher Wagner noticed: "There was no evidence of either less carcinogenicity or less asbestosis in the groups exposed to chrysotile than those exposed to the amphiboles" [84]. Chrysotile was found to be even more carcinogenic than amphiboles in a study, 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" [84]. Technical details of the study [84] were discussed by Bernstein et al. [67] but not this essential conclusion. In one rat study, chrysotile induced more lung fibrosis and tumors than amphiboles [88]. Chrysotile induced chromosomal aberrations and pre-neoplastic transformations of cells in vitro [83,89].

In humans, the LC risk difference between chrysotile vs. amosite and crocidolite was estimated in the range from 1:10 to 1:50. The risk ratio of mesothelioma was estimated, respectively, as 1:100:500 [90], cited in reviews [35,91]. In a subsequent publication, the ratio 1:5:10 was suggested [92]. The same researchers [90] acknowledged that, in view of the fact that different asbestos types produced a similar harvest of lung tumors in animal experiments [66], it is difficult to reconcile 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)" [90]. However, there are no reasons to suppose substantial interspecies differences in the fiber clearance mechanisms. Experiments with larger animals could clarify the matter. As mentioned above, the chrysotile clearance from the lung may partly result from the fiber splitting and migration to the pleura. As for epidemiological studies, some of them are biased due to the screening effect with overdiagnosis in exposed populations, unclear demarcation of MPM from other cancers, imprecise exposure histories and, last but not least importantly, conflict of interest in researchers associated with the chrysotile industry.

The well-known review [66], not cited by Bernstein et al. [60,67],

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concluded that animal experiments indicate an approximately equal risk associated with all asbestos types: "Even if one accepts the argument that chrysotile asbestos does not induce mesothelioma (which we do not), the risk of LC (and asbestosis) cannot be dismissed, and chrysotile appears to be just as potent a lung carcinogen as the other forms of asbestos" [66]. Moreover, "Bernstein and colleagues completely ignored the human lung burden studies that refute their conclusion about the short biopersistence of chrysotile" [71]. In their reply to [71], Bernstein and co-workers dismissed the arguments with the remark that the studies [93,94] "appear to support the concepts put forward by Bernstein et al." [95]. Numerous relevant publications e.g. [62-66,68,76,77,83,93], unsupportive of his conclusions, were not cited in Bernstein's reviews [60,67]. Another example: Bernstein et al. [67] cited the phrase from the review titled "Mesothelioma from chrysotile asbestos" that chrysotile is an "overwhelming fiber exposure" [96] but not the essential conclusion: "Chrysotile asbestos, along with all other types of asbestos, has caused mesothelioma" [96]. 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 [68,71].

The toxicity of fibers is generally determined by the three "D's": dose, dimension and durability; thin and long fibers tending to be more carcinogenic [9,97-99]. The biopersistence being equal, differences in carcinogenicity are associated with the fiber length [67,100]. Long fibers of chrysotile were found to possess a relatively high toxicity as they cannot be efficiently engulfed and cleared by phagocytosis [101,102]. According to another report, thin short chrysotile fibers were found to be prevailing in the lung and pleura of patients with MPM [103]. Differences in carcinogenicity between short and long fibers are not entirely clear; further independent research is needed. In addition, tremolite admixture in chrysotile products can potentiate carcinogenicity [84]. A review concluded that there is no compelling evidence that the increased incidence of MPM in chrysotile workers was caused solely by tremolite [66]. In one epidemiological study, the difference in MPM risk between pure chrysotile and its mixtures with amphiboles was insignificant [104].

The question of relative potency of different asbestos types was examined in a meta-analysis of 19 epidemiological studies evaluating the impact of research quality on exposure-response estimates for LC [91]. The difference in carcinogenic potency between chrysotile and amphiboles was hard to ascertain when the meta-analysis was restricted to studies with fewer exposure assessment limitations [91] i.e., to those of higher quality. After accounting for quality, there was little difference in the exposure-response slopes for chrysotile compared to amphiboles [91,105]. According to a systematic review, pooled risk estimates for LC were higher after exposures to amphiboles (1.74) than to chrysotile (0.99). However, the overall risk tended to be higher in intermediate- rather than in high-quality studies (there was no poor-quality group): 1.86 vs. 1.21 [106]. Significant differences between results of high- vs. low-quality studies are indicative of a conflict of interest, as it is obviously easier to find support for preconceived ideas in poor-quality and manipulated studies than in high-quality research. After all, amphiboles are probably more carcinogenic than chrysotile, but further independent research is needed to quantify the difference.

Discussion

Undoubtedly, asbestos is a carcinogen. However, some epidemiological research is biased due to the screening effect with overdiagnosis in risk groups, imprecise exposure histories and conflicts of interest. The number of publications about asbestos is growing; and it is difficult to distinguish between reliable and unreliable reports. There is an opinion that "grassroots organizations intimidated governments into approving more restrictive regulations" [107]. Apparently, some environmental campaigners serve certain governments or companies, which has been discussed also in regard to the nuclear energy and boosting fossil fuel prices [1]. Citizens should be aware that their best intentions may be exploited to disadvantage their nations. Asbestos is prohibited in some countries while others augment production [108]. Different fiber types may be intermixed in the international trade [109]. Carbon nanotubes, metal nanowires and other artificial fibers are also associated with health risks. By analogy with asbestos, their carcinogenicity is largely dependent on dimensions, durability and mechanical properties of the fibers [17,19,110,111]. The most promising way to reliable information would be lifelong bioassays. Experiments with fiber inhalation, using doses comparable to industrial exposures, do not require invasive methods thus being ethically acceptable. Bioassays with "exposure concentrations that were orders of magnitude greater than those reported for worker exposure" [112] are of limited conclusiveness.

Asbestos is used in the industry and construction due to its high thermal, electrical and chemical resistance [113]. Different asbestos forms have their advantages and preferred application areas. Amphiboles are acid-resistant, thermo-stabile and durable [114]. This is an additional reason in favor of the "All Fibers Equal" [115] concept in regard to asbestos and some other fibers. Considering industrial interests behind chrysotile, and possibly also some artificial fibers, any deviations from the All-Fibers Equal approach must be based on high-quality, independent research.

Conclusion

Studies of human populations exposed to low doses of noxious agents such as asbestos or ionizing radiation, though important, will hardly add much reliable information on dose-effect relationships. Screening effect, selection, self-selection and ideological biases will contribute to appearance of new reports on enhanced risks, which would not prove causality. Reliable results can be obtained in lifelong animal experiments. The life duration is a sensitive endpoint attributable to various exposures, which can measure the net harm, if any, from low-dose exposures. The fireproofing properties of asbestos are well known. Asbestos cement (fibrolite) constructions are sturdy and inexpensive; their use increased during the World War II. The non-use of asbestos-containing construction materials, brakes, fireproofing and insulation laggings would weaken defenses of civilized nations, enhance the damage from traffic accidents, fires and armed conflicts. Today, in view of the international tensions, the attitude to asbestos should be changed.

Conflicts of Interest

The author declares that he has no conflicts of interest.

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