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Asbestos, Mesothelioma and Lung Cancer: A Comment

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ABSTRACT

This short communication continues and summarizes previously published articles. Asbestos-related risks have been estimated on the basis of extrapolations from the past, when high-dose exposures were more frequent. The linear no-threshold dose-response pattern has been assumed for low exposure levels although its applicability has never been proven. Inhalation and discharge of fibers are normally in a dynamic equilibrium. Accordingly, there may be a safe exposure level (threshold). The screening bias probably contributed to the enhanced registered incidence of asbestos-related diseases in exposed populations. In particular, mesothelioma was sought in exposed populations and correspondingly more often found. Malignant mesothelioma is indistinctly demarcated as an entity; in asbestos-exposed populations, questionable or borderline cases can be diagnosed as mesothelioma. Furthermore, carcinogenicity of chrysotile vs. amphibole asbestos is discussed. Research on this topic has been influenced by economic interests. Chrysotile clearance from the lung may partly result from the fiber splitting and movement to the pleura. A possible way to objective information may be large-scale chronic bioassays. In conclusion, the asbestos-related policies should be revaluated on the basis of independent research.

***Key Words*:** amphibole, asbestos, chrysotile, mesothelioma, lung cancer

INTRODUCTION

Asbestos-related risks have been estimated on the basis of extrapolations from the past, when high-dose exposures were more frequent. The linear no-threshold dose-response pattern has been assumed for low exposure levels although its applicability has never been proven. In some places, asbestos fibers are present in the natural environment due to erosion of surface deposits. Naturally occurring asbestos has been commonly found in populated areas. [1] Asbestos fibers were found in the lungs of >60% deceased people from the general population, also in children. [2,3] Inhalation and discharge of fibers occur normally [4] being in a dynamic equilibrium. Accordingly, there may be a safe exposure level (threshold) or even hormesis. Existence of a threshold may be assumed by analogy with other factors that have induced evolutionary adaptation; more discussion in. [5,6] The concept "one fiber can kill" may have as little relevance to reality as it is for environmental levels of numerous substances and physical factors that would be toxic at higher doses.

By analogy with radiation-related diseases, [7] the screening effect probably contributed to the enhanced registered incidence of asbestos-related diseases in exposed populations and exaggeration of dose-response relationships. In particular, mesothelioma was sought in exposed populations and correspondingly more often found. Mesothelioma can be spontaneous and/or occur when asbestos fibers are present in the pulmonary or pleural tissue, which does not necessarily mean a cause-effect relationship. Apart from asbestos, potential etiologic factors of malignant mesothelioma (MM) include mineral and artificial fibers, virus SV40, ionizing radiation and genetic predisposition. [8-15] SV40-like DNA sequences have been regularly found in MMs; more details and references are in. [16] when hamsters were injected with SV40 into the pleural space,

all of them developed mesotheliomas within 3-6 months. [17] It can be reasonably assumed that invasive manipulations e.g. bronchoscopy in people exposed to asbestos could have contributed to dissemination of SV40 as it occurs with hepatitis virus. [18] In the former SU, bronchoscopy and bronchial biopsy were performed and recommended in patients with asbestos-related bronchitis sometimes without clear indications and resulting in no specific findings; [19,20] more details are in. [21]

Histologically, MM can resemble various cancers while the lack of specific biomarkers makes diagnosis difficult. Cancers can undergo de-differentiation, becoming histologically similar to MM. The differential diagnosis varies depending on the tumor subtype. Spindle cell tumors of the pleura are particularly difficult to differentiate while immunohistochemistry may be of limited help. [15,22,23] Misdiagnosis of MM is a worldwide problem [24,25] revisions of histopathological archives found inaccurately classified cases, while in a considerable percentage of cases no clear-cut entity diagnosis was possible despite extensive application of immunohistochemistry. [23,24] For example, in France, the initial pathologists' diagnosis was confirmed in 67% of cases, ruled out in 13%, and left uncertain in others; for half of the latter, the clinical findings supported a mesothelioma diagnosis. [26] According to an estimate, about 10% of MMs are misdiagnosed in the U.S. [24] among reasons is insufficient experience due to the rarity of MM in the general population. [23,24] On the contrary, in asbestos-exposed populations pathologists perform well-aimed search for MM. Accordingly, more cases are found, questionable or borderline cases being sometimes diagnosed as MM.

Lack of accurate biomarkers makes diagnosis of MM challenging. [15] Mesothelin has been discussed as one of the most promising biomarkers for MM. [27] However, it is over expressed in several cancers including lung adenocarcinoma. [28] Mesothelin is not sufficiently sensitive for diagnostics. [15,27,29] Sarcomatoid MM rarely expresses mesothelin. [23] A panel that includes calretinin, WT-1, pankeratin, TTF1, P63, Moc31, CEA and PAX8 was recommended to help differentiating MM from carcinomas. [23] However, a tumor diagnosed as MM using panels and algorithms is not necessarily biologically different from other cancers. The validity of biomarkers is sometimes exaggerated due to the push for discoveries by researchers and sponsors. [27] The microRNA down-regulation in MM compared to lung cancer was regarded to be a promising marker; [30,31] however, microRNA are deregulated also in some other cancers. [31-33] MM has heterogeneous and even chaotic chromosomal aberrations, [11,34,35] which contributes to its indistinct demarcation as an entity and increased detection in case of screening and well-aimed search.

Bias is not infrequent in asbestos research, e.g. detection of fibers in pulmonary or pleural tissues attributing the neoplasm to asbestos, although a cause-effect relationship remains unproven. [36] As mentioned above, asbestos fibers, possibly originating from natural sources, are often found in pulmonary tissues of people having no professional exposure history. Some studies rely on work or residence histories of questionable reliability, interviews with relatives, etc. Bias due to litigation may further compromise objectivity. [36]

Asbestos-related diseases have been studied in former Soviet Union (SU), although the interest seems to have dwindled since the last years together with the number of publications. The prevailing opinion is that, if necessary precautions are observed, modern technologies of asbestos production and processing are acceptably safe, whereas bans and prohibitions applied in some countries are excessive. [37,38] Health hazards from low fiber concentrations are unproven. No enhanced risks have been demonstrated in residents near modern asbestos-processing factories. [39,40] Epidemiological studies indicate the presence of a threshold; [39,40]

a genetic adaptation to a certain level of asbestos fiber inhalation is deemed possible. [41]

In the SU, corrugated asbestos sheets have been broadly used for roofing being often sawn by hand. However, fiber emission from roofing materials during construction and use of buildings under the influence of both natural and anthropogenic factors is regarded to be negligible. [42] Fiber concentrations in the indoor air are an order of magnitude below the maximum permissible level. [42] Asbestos-cement pipes have been routinely used for drinking water distribution deemed safe as no risks from oral intake of fibers have been proven, the more so as fibers in asbestos cement are modified by connection with cement particles. [43,44] Asbestos-containing broken-stone ballast – a by-product of chrysotile enrichment – has been used for gravelling of railroad embankments while enhanced concentration of airborne fibers was noticed both in trains and in nearby townships. [45]

Similarly to asbestos-cement, carcinogenicity of fibers in asbestos board is decreased due to connection with starch. [46] Toxic effects from brake linings with and without asbestos do not differ significantly; there is no considerable air pollution from asbestos-containing brake linings, while the traffic safety tends to be higher with asbestos-containing linings. [47,48] In the process of car braking, asbestos is transformed to forsterite, which is largely harmless. [49,50] Other 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 at workplaces is deemed safe. [48]

No increase in the registered incidence of mesothelioma has been found either in asbestos workers or residents of the areas with asbestos industry. [51] It was concluded on the basis of analysis of 3576 MM in Russian Federation that asbestos is neither a leading nor obligate causative factor. [52] Among 69 cases studied in Kazakhstan, asbestos exposure was detected in no one; geographic association of mesothelioma was found neither with asbestos mining nor with processing industry. [53]

Some experts in the former SU admitted that the concept of much higher toxicity of inhaled amphibole fibers compared to chrysotile has not been confirmed. [54] Carcino-, fibro-, mutagen city and cytotoxicity of chrysotile was confirmed both in experiments and epidemiological studies. [55-57] In experiments, chrysotile was reported to possess acute toxicity, inducing the granulomatous tissue reaction; [58] its carcinogenicity did not differ significantly from that of the amphiboles. [59] At the same time, there are strong industrial interests behind chrysotile. Accordingly, statements in favor of chrysotile (sometimes without references) can be encountered, [60,61] for example: “Chrysotile fibers are easily dissolved and discharged.” [61]

Papers by David Bernstein [62,63] generally agree with Russian literature e.g. “Following short-term exposure the longer chrysotile fibers rapidly clear from the lung and are not observed in the pleural cavity”; [62] more citations are in. [64] Of importance is, however, the fiber retention in pleural and pulmonary tissues, not in the cavity. Given the possibility of a post-depositional movement of chrysotile fibers from the lung to pleura, [65-70] the rate of asbestos retention cannot be determined only by measurements of fiber contents in pulmonary tissues. On the contrary to the amphiboles, chrysotile fibers were shown to accumulate predominantly in the parietal pleura rather than in the lung. [65] Moreover, the accelerated clearance of chrysotile from the lung can be partly caused by disintegration of chrysotile fibers into thin fibrils, which can escape identification. The total number of fibrils would increase due to the fiber splitting [69,71,72] possibly together with an increase in carcinogenic potency, the more so as the fibrils can move to the pleura. [67,69,70] Asbestos fibers are found in the pleura post mortem, chrysotile being the

predominant fiber type in pleural plaques [73] and pleural tissues in general. [68,74] The concept of fiber migration to the pleura agrees with the fact that the primary affect of asbestos-related mesothelioma is usually found in the parietal rather than visceral pleura. [75]

Conclusions by Bernstein et al. [62,76] about low biopersistence of chrysotile fibers are supported by numerous self-references; however, results of their experiments are at variance with other data and can be explained by a chemical pre-treatment of fibers, inducing their hydration, fragility and breaking. [77] 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; [78] both chrysotile and crocidolite showed very low solubility. The dissolution values 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). On the contrary, aramide and carbon fibers were practically insoluble. [78] This indicates that certain artificial fibers, proposed as asbestos substitutes, are chemically more stable than asbestos. The study [78] was referenced but not discussed by Bernstein. [76]

Chrysotile induced chromosomal aberrations and pre-neoplastic transformations of cells in vitro. [79,80] In certain animal experiments, the amphiboles and chrysotile were shown to be nearly equally carcinogenic for both mesothelioma [72,79,81,82] and lung cancer. [83,84] Chrysotile was found to be even more carcinogenic than amphiboles by the study, [81] 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." [81] Technical aspects of the study [81] were discussed by Bernstein [76] but not this essential result. According to, [85] chrysotile asbestos produced far more lung fibrosis and tumors than amphiboles, which was explained by a larger fraction of fibers longer than 20 μm in the chrysotile dust used in this experiment. 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. [8,86-88] It was noticed that potency differences of chrysotile vs. amphiboles are difficult to ascertain when meta-analyses are restricted to studies with fewer exposure assessment limitations. [89] After accounting for the quality of exposure assessment, there appeared to be little difference in the slopes for cumulative exposure to chrysotile compared to amphibole fibers. [90] Epidemiological data are not uniform: for example, no mesothelioma incidence increase was found in people who had contact with crocidolite in Bolivia. [91,92] The supposed difference in toxicity e.g. between Bolivian and South African chrysotile could have been caused not only by different fiber width, as supposed in, [91] but also by different attitude of researchers exemplified below.

J. Christopher Wagner was the first scientist who emphasized the association between crocidolite and MM. His research was pivotal in the introduction of the banning of crocidolite. [92] Association of mesothelioma with crocidolite was advocated by Wagner mainly on the basis of epidemiologic data, [93] although it was partly at variance with his own experiments. [81,82] The epidemiological data were obtained from crocidolite-exposed workers, where the relatively large number of MMs could have been caused by a well-aimed search and higher exposures to asbestos before the 1960s considering the long latency period. It may be reasonably assumed that Wagner worked in accordance with the interests of chrysotile producers. A parallel with another researcher, David Bernstein, seems to be justified.

The well known review, [68] not cited in Bernstein's reviews, [62,76] 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 lung cancer (and asbestosis) cannot be dismissed, and chrysotile appears to be just as potent a lung carcinogen as the other forms of asbestos." [68] Moreover, "Bernstein and colleagues completely ignored the human lung burden studies that refute their conclusion about the short bio persistence of chrysotile." [94] The reports [95-97] on chrysotile fibers persisting in the lungs and their association with MM or carcinoma were not cited in Bernstein's reviews. [62,76] In his reply to the comment, [94] Bernstein left the essential arguments without response, dismissing them with the remark that the studies [95,98] "appear to support the concepts put forward by Bernstein et al." followed by self-references. [99] Numerous relevant papers, [65-70,73,74,77,79,100-102] unsupportive of Bernstein's opinions, were not cited in his reviews. [62,76] Another example: Bernstein et al. [76] cited the phrase from the review "Mesothelioma from chrysotile asbestos" [51] that chrysotile is an "overwhelming fiber exposure" [103] but not the principal conclusion: "Chrysotile asbestos, along with all other types of asbestos, has caused mesothelioma." [103] 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 have published a document to support the interests of chrysotile producers. [77,94] It should be added that some papers by Bernstein et al. sound remarkably similar to Russian publications promoting chrysotile. [60,61]

The author shares the opinion that asbestos bans have been partly based on research influenced by political and economical interests, while grassroots intimidated governments into approving more restrictive regulations. [104] it was the aim of this review to point out that some anti-asbestos activists apparently served certain governments or companies. The same is partly true also for the anti-nuclear activism and the Green movement in general. [105,106] Citizens should be aware that their best intentions may be exploited to disadvantage their countries.

Among others, the high incidence of mesothelioma in workers exposed to crocidolite could have been caused by insufficient control for potential differences in exposure levels. [107] Associations between mesothelioma incidence, time of the first exposure and the total exposure [108] can be explained by the screening bias, dose-related differences in medical surveillance and self-reporting – analogously to some radiation-related conditions. [6,7] There is considerable evidence that the risk of mesothelioma is enhanced after exposures to chrysotile without amphibole admixture. [68,70,96,101,102,109] Corroboration of some statements is questionable e.g. that the exposure-specific risk of mesothelioma from three asbestos types (chrysotile, amosite, crocidolite) is in the ratio 1:100:500. [110] in a later paper by the same authors, quite another ratio was proposed: 1:5:10; [111] more discussion is in. [64]

According to the reports, [68,83,84] there is no epidemiological or toxicological evidence that chrysotile is less potent than other forms of asbestos for induction of lung carcinoma, which is essential because of its much higher incidence compared to that of mesothelioma. Admittedly, the ratio between lung cancer risks from exposures to chrysotile and amphiboles was estimated to be between 1:10 and 1:50. [110] However, the same researchers [110] acknowledged that, in view of the evidence that different asbestos types produced a similar harvest of lung tumors in animal experiments, [68] 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 fibers (cleared in years)." [110] It was the purpose of this comment to question this concept: chrysotile clearance from the lung may partly result from the fiber splitting and movement to the pleura; while epidemiological studies can be prone to a

systematic error due to the screening effect, biased exposure histories, unclear demarcation of mesothelioma from other cancers, over-diagnosis in exposed populations and, last but not least, industrial interests.

Asbestos research has been influenced by economical and political interests, aimed in particular to promote chrysotile. [112] the quality of research, potential bias and conflict of interest should be taken into account defining inclusion criteria for studies into reviews. A possible way to objective information may be large-scale chronic bioassays using larger animals including primates. [113] such experiments may lead to identification of threshold exposure levels for different fiber types. Even hormesis cannot be excluded a priori. The bioassays with fiber inhalation, comparable to exposures in the asbestos industry, can be performed without invasive procedures, which would be ethically acceptable. However, animal experiments are permissible only in conditions of integrity of all participants.

According to the IARC, chrysotile causes lung carcinoma, mesothelioma and asbestosis. [109] Different asbestos types can be mixed in the international trade. [114] As mentioned above, carcinogenic effects depend not only on biopersistence but also on dimensions of fibers of different types, [8,86-88] which is an additional argument in favor of the All Fibers Equal approach to asbestos and its substitutes. This concept can be used provisionally, pending reliable evidence. The All Fibers Equal basis of safety regulations is technically most plausible, being partly compatible with current knowledge conflicting as it is. Considering the strong economic interests behind chrysotile, [112,115,116] and newly also some artificial fibers, any deviations from the All Fibers Equal [16] concept must be based on high-quality, independent research. Substitution of asbestos by artificial fibers would not necessarily eliminate health risks. [8-10,117,118] the stable or increasing incidence of MM in developed countries despite the anti-asbestos measures is probably at least in part caused by increasing awareness, improvements of diagnostic equipment, screening effect in asbestos-exposed populations, and some over-diagnosis in view of the unclear demarcation of MM as an entity. [119] In conclusion, the bans and restrictions of asbestos should be revaluated on the basis of independent science. Most importantly, asbestos-related research must be separated from industrial interests. [120]

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