INTRODUCTION

Asbestos-related risks have been estimated on the basis of extrapolations from the past, when high-dose occupational exposures were frequent. The linear no-threshold (LNT) dose-response pattern has generally been assumed for the low exposure levels. However, applicability of the LNT hypothesis to low asbestos exposures has never been proven. Asbestos fibers are present in the natural environment in some places due to erosion of surface deposits. Inhalation, degradation and discharge of the fibers occur normally [1,2], probably being in a dynamic equilibrium. Existence of a threshold “no-effect” level for the exposure to mineral fibers has not been demonstrated so far, but can be assumed by analogy with other environmental factors that have induced evolutionary adaptation [3,4]. Certainly, this supposition cannot be adopted as a working hypothesis without verification in large-scale bioassays. Research into nonlinear, threshold cancer risk models is warranted not only for chrysotile [5], but also for other forms of asbestos and its man-made substitutes.

ASBESTOS AND MESOTHELIOMA

The screening effect must have contributed to the enhanced registered incidence of asbestos-related diseases in the exposed populations and hence to overestimation of the dose-response relationship. In particular, malignant mesothelioma was sought among exposed people and correspondingly more often found. Mesothelioma is an uncommon neoplasm developed by a small percentage of people exposed to asbestos. It can be spontaneous also if asbestos fibers are present in pulmonary or pleural tissues. Apart from asbestos, other causative factors of malignant mesothelioma are known: Certain mineral fiber (erionite), artificial fiber (carbon nanotubes, ceramic fiber) [6-8], Simian virus 40, ionizing radiation, and inheritance of predisposing genes [9-12].

The diagnosis of malignant mesothelioma is not always straightforward. Histologically, mesothelioma can resemble various cancers. Some studies may have mistakenly included tumors that resemble mesothelioma [12]. Metastatic cancers can undergo desmoplastic transformation thus becoming histologically similar to mesothelioma [13]. The histological and immunohistochemical differential diagnosis of mesothelioma is complicated and depends on its type, e.g. for the epithelioid variety it includes carcinomas and epithelioid malignancies, for the sarcomatoid variety-sarcomas and other spindle cell neoplasms, for biphasic mesothelioma-synovial sarcoma [14]. There are standard diagnostic algorithms in histopathology; however, a tumor diagnosed by the standard methods as mesothelioma is not in all cases substantially different from other cancers. Cytogenetic studies found out that malignant mesothelioma has complex and even chaotic chromosomal aberrations [9,15,16]. No marker performs well in discriminating between mesothelioma and other cancers [17]. Together with uncertainty about progenitor cells [9], it makes the definition of mesothelioma as an entity indistinct. Recent studies have not changed much in this regard.

ABSTRACT

Asbestos manufacturing and trade are prohibited by some countries while others continue to increase production and exports. Substitution of asbestos by artificial fibers would not necessarily lower the health risks. The incidence growth of malignant mesothelioma in recent years in developed countries, in spite of the bans and prohibitions of asbestos, is probably at least in part caused by a screening effect in asbestos-exposed populations and overdiagnosis in conditions of indistinct delineation of mesothelioma as an entity. The tumor diagnosed by the standard methods is not in all cases substantially different from other cancers. Furthermore, favoring of chrysotile asbestos when compared to amphiboles is at least in part caused by economic interests. Arguments in favor of the “all fibers equal” approach to the regulations applied to asbestos and its man-made substitutes are discussed here. In conclusion, bans and restrictions applied by some countries to the asbestos trade, manufacturing and use should be revised on the basis of independent research.

KEY WORDS: amphibole, asbestos, chrysotile, mesothelioma, lung cancer
Soluble mesothelin and osteopontin have been considered promising markers for pleural mesothelioma, but are subject to limitations [18,19]. Although several studies indicated that the mesothelin is useful in screening for early signs of the disease, other evidence witnessed that this marker is not useful due to the high false-positivity rate [20,21]. Osteopontin serum concentration is not deemed an adequate diagnostic marker because of false-positivity and lacking specificity to differentiate between pleural mesothelioma and metastatic carcinoma [22]. Furthermore, DNA methylation as a diagnostic marker was criticized because in pleural mesothelioma it depends on age, ethnicity and histologic subtype [20]. Data on downregulated microRNAs in mesothelioma when compared to lung cancer [20,23] seem to be promising for better delineation of malignant mesothelioma as an entity and its demarcation from carcinoma. However, miRNAs are often deregulated in cancer [24], so that high specificity of this marker a priori appears to be questionable, and misclassifications are not excluded [25]. If the reported high specificity of the miRNA essay in discrimination mesothelioma vs. carcinoma [25,26] will be confirmed by further research, it could be used e.g. for re-evaluation of archives of histological specimens to estimate percentage of mesothelioma over diagnosed in the past, the more so as miRNAs can be detected in formalin-fixed paraffin-embedded tissues [27].

Finally, biases and confounding factors are frequent in the mesothelioma asbestos research, for example, determining of small amounts of fiber in pulmonary or pleural tissues; and if found, attributing the tumor to asbestos [28]. Conflicts of interest related to litigation and benefits in case of recognition of an occupational disease further contribute to the biases. Some studies rely on work histories of questionable reliability, interviews with friends and relatives of deceased patients, etc. [28].

CHRYSO TILE VERSUS AMPHIBOLES

In regard to the carcinogenicity of asbestos, there is considerable evidence from earlier studies, reviewed, e.g., in [29,30], that chrysotile is as active as crocidolite and amosite in inducing lung cancer and mesothelioma. Chrysotile was shown to be toxic, caused chromosomal aberrations, and induced pre-neoplastic transformations of cells [29,30]. Animal experiments generally confirmed that all major asbestos varieties produce lung cancer and mesothelioma with limited differences in carcinogenic potency [30].

Asbestos-related diseases have been extensively studied in the former Soviet Union. The prevailing view in Russian professional literature has been that, if necessary precautions are observed, modern technologies of asbestos manufacturing and processing are acceptably safe, while bans and prohibitions applied by some countries are excessive [31,32]. A review of 3,576 mesothelioma cases concluded that chrysotile asbestos had been neither leading nor obligate cause [33]. Among 69 mesothelioma cases from Kazakhstan, asbestos exposure was detected in no one of them [34]. Some researchers admitted that the concept of much higher carcinogenicity of the amphibole compared to serpentine (chrysotile) asbestos has not been confirmed [35]. At the same time, there are strong economical interests to promote chrysotile because of its abundant deposits in Russia. Accordingly, statements in favor of chrysotile, sometimes without references, can be encountered [36,37], for example: “Chrysotile fibers are easily dissolved and discharged” [37]. Considering possible translocation of chrysotile fibers from lung to pleura [38-41], statements of this kind are oversimplifications. Decomposition by acids does not necessarily mean easy solubility in living tissues. High solubility of chrysotile was reported in animal studies by Bernstein et al. summarized in [2]. It was however commented that chrysotile-related research has been influenced by the industry, that Bernstein’s reports contradict results obtained by independent scientists and can only be explained by a pre-treatment, inducing structural damage and fragility of the fibers, contributing to hydration and breaking of long fibers [42].

D i f f e r e n t types of fibers were tested for solubility in the Gamble’s solution, which is similar in composition to lung fluid except for organic components [43]. Solubility of both chrysotile and crocidolite was designated as very low. The dissolution values ranged from a few ng cm\(^{-2}\) of dissolved silicon (chrysotile and crocidolite) to several thousands of ng cm\(^{-2}\) (glass wools). On the contrary, aramide and carbon fibers were demonstrated to be practically insoluble [43]. It shows that certain artificial fibers, proposed as asbestos substitutes, are less soluble than asbestos. Note that carcinogenicity and other toxic properties of fibers depend on their biopersistence and dimensions (length, diameter, size-specific fractions) [2,6,20,44]. For example, it was shown that increased lung cancer mortality among chrysotile asbestos textile workers is more strongly associated with exposure to long thin fibers [45], a finding that can probably be generalized to different kinds of fibers.

The rate of asbestos retention in parietal pleura cannot be characterized solely on the basis of measurements of fiber contents in pulmonary tissues: The proportion of chrysotile fibers (as opposed to amphiboles) was shown to be higher in parietal pleura than in lung tissue [38]. Moreover, the accelerated clearance of chrysotile from the lung can be partly caused by the disintegration of chrysotile (but not amphibole) fibers into thinner fibrils, which are more difficult to identify and to count by electron microscopy. In this way, the total number of fibers is increasing [45-47], probably together with carcinogenicity. After the splitting, the fibrils can move to pleura [40,47]. Note that the initial affect of asbestos-related mesothelioma usually is in the parietal rather than visceral pleura [48].

In contrast to lung cancer, there has been epidemiologic evidence indicating that the chrysotile is less potent than amphiboles with regard to the induction of mesothelioma. Association of mesothelioma with crocidolite and tremolite as opposed to chrysotile was advocated by J. Christopher Wagner [49] mainly on the basis of epidemiologic data, propagating the difference between white vs. blue and brown asbestos, although it was contradictory to the results of his own experiments [50]. The epidemiologic data were partly from crocidolite-exposed populations in Southern Africa, where the relatively large number of registered mesothelioma cases could
have been caused by the well-aimed search as well as working and housing conditions in the 1920-50s considering the latency period of mesothelioma ranging between 20 and 60 years [20]. Furthermore, the greater incidence of mesothelioma in workers exposed to crocidolite could have been related to the lack of control for potential differences in exposure levels [51]. There is abundant evidence that the risk of mesothelioma is enhanced after exposure to chrysotile also without amphibole admixture [41,52-56], although there is also the opposite view [57,58]. There is no epidemiological or toxicological evidence to support the argument that chrysotile asbestos is any less potent than other forms of asbestos for inducing lung cancer [41,59,60], which is essential because of the much higher incidence of lung cancer compared to malignant mesothelioma.

Therefore, in the author’s opinion, there is no sufficient evidence in support for separate regulations for serpentine (chrysotile) and amphibole asbestos. The US Environmental Protection Agency and the Agency for Toxic Substances for Disease Registry deem “all fibers equal” in toxicity [61]. Different asbestos types can be mixed in the international trade: For example, in some chrysotile products from China the levels of amphibole admixtures were found to be substantial [62]. The “all fibers equal” concept in regard to the asbestos-related regulations would be not only the most practicable one, but also largely compatible with the current knowledge, conflicting as it is [63,64]. Considering strong economical interests behind the “chrysophile versus chrysophobe” [65] debate, deviations from the “all fibers equal” approach to the regulations applied to asbestos and its man-made substitues, if any, must be based on reliable independent research.

CONCLUSION

Current asbestos-related regulations are irrational: Asbestos manufacturing and trade are prohibited by some countries, while others continue to enlarge production and exports. At the same time, substitution of asbestos by artificial fibers would not necessarily lower the health risks [66]. The “alarming” [26] incidence growth of mesothelioma in recent years in developed countries of Western Europe, North America and Japan [26,67,68], in spite of the bans and prohibitions of asbestos, is probably at least in part caused by increased awareness, screening effect in asbestos-exposed populations as well as over-diagnosis in conditions of unclear delineation of malignant mesothelioma as an entity. Biases are not excluded in mesothelioma-asbestos research, for example, detecting of small amounts of fiber in the lung, and if found, attributing the lesion to asbestos. Screening effect must have contributed to enhanced registered incidence of asbestos-related diseases in the exposed populations and therefore to overestimation of the dose-response relationship. Furthermore, favoring of chrysotile asbestos when compared to amphiboles is again at least in part caused by economical interests of chrysotile-producing countries. Accelerated clearance of chrysotile fibers from the lung can be partly explained by the spitting of the fibers and their preferential translocation to pleura. Most importantly, asbestos-related research should be separated from industrial interests. In conclusion, bans, and restrictions applied by some countries to the asbestos trade, manufacturing and use should be revised on the basis of independent research.

REFERENCES

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