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Non-asbestiform elongate mineral particles and mesothelioma risk: Human and experimental evidence

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Abstract

The presentations in this session of the Monticello II conference were aimed at summarizing what is known about asbestiform and non-asbestiform elongate mineral particles (EMPs) and mesothelioma risks based on evidence from experimental and epidemiology studies. Dr. Case discussed case reports of mesothelioma over the last several decades. Dr. Taioli indicated that the epidemiology evidence concerning non-asbestiform EMPs is weak or lacking, and that progress would be limited unless mesothelioma registries are established. One exception discussed is that of

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taconite miners, who are exposed to grunerite. Drs. Mandel and Odo noted that studies of taconite miners in Minnesota have revealed an excess rate of mesothelioma, but the role of non-asbestiform EMPs in this excess incidence of mesothelioma is unclear. Dr. Becich discussed the National Mesothelioma Virtual Bank (NMVB), a virtual mesothelioma patient registry that includes mesothelioma patients' lifetime work histories, exposure histories, biospecimens, proteogenomic information, and imaging data that can be used in epidemiology research on mesothelioma. Dr. Bernstein indicated that there is a strong consensus that long, highly durable respirable asbestiform EMPs have the potential to cause mesothelioma, but there is continued debate concerning the biodurability required, and the dimensions (both length and diameter), the shape, and the dose associated with mesothelioma risk. Finally, Dr. Nel discussed how experimental studies of High Aspect Ratio Engineered Nanomaterials have clarified dimensional and durability features that impact disease risk, the impact of inflammation and oxidative stress on the epigenetic regulation of tumor suppressor genes, and the generation of immune suppressive effects in the mesothelioma tumor microenvironment. The session ended with a discussion of future research needs.

Keywords

Elongate mineral particle (EMP); Asbestos; Cleavage fragments; High aspect ratio engineered nanomaterials; Mesothelioma

1. Introduction

Bank (1980), who identified more than 150 types of fibrous minerals found in mines, mills, and quarries, was an early user of the term elongated mineral particles (EMP). His goal was to identify fibrous minerals besides asbestos that might cause disease. Fibrous morphology was considered an important property, imparting fibrogenic and carcinogenic potential to minerals, and at that time concerns were raised about the health hazards of other EMPs (Stanton et al., 1981; Nolan and Langer, 1993). The potential for other fibrous minerals to be pathogenic was heightened by the observation that commercial asbestos minerals, with diverse elemental compositions, were presenting similar disease patterns, although often with markedly different potencies.

Fibrous minerals form their morphology when the crystals grow. An elongate morphology can sometimes form from the crushing of the massive habit of non-asbestos minerals, although usually this results in widths or aspect ratios that are different than those of fibers. EMPs are mineral particles with an aspect ratio of ≥3, meaning that the length of the particle exceeds its width by a factor of at least 3. This term does not address the length or width (other than in connection with the aspect ratio), habit, chemical composition, or other characteristics of a particle. EMPs include both non-asbestiform and asbestiform particles.

The asbestiform analogs of the six minerals listed in Table 1 are those currently regulated as asbestos in the United States (US) and most countries. Chrysotile is the only form of serpentine mined as asbestos. It has historically represented more than 90% of the asbestos produced commercially. Asbestos and non-asbestos analogs are represented by different Chemical Abstract Service (CAS) Numbers, as they are recognized as different

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substances. The three serpentine minerals are polymorphs, having almost identical elemental composition but differing in structure (Demichelis et al., 2016), while the amphibole asbestos minerals have similar structures but diverse elemental compositions. Production of the amphibole asbestos minerals (chiefly crocidolite, amosite, and anthophyllite asbestos) had left commerce by the late 1990s. Only chrysotile remains in commercial use with worldwide production of about 2 million tons per year, primarily from Russia, Kazakhstan, and China.

In this paper, asbestos refers specifically to the six regulated minerals listed in Table 1, which have been used commercially and all the asbestos minerals can be described as asbestiform. Although some authors have used the term “asbestos” to refer to the non-commercial asbestiform amphibole (Wylie and Huggins, 1980; Wylie and Verkouteren, 2000; Vigliaturo et al., 2021), this is contested by others. Further, CAS Numbers for the asbestiform minerals are different from those of the non-asbestos amphiboles of similar elemental composition due to their markedly different morphologies (Table 1).

Asbestiform minerals form as polyfilmentous bundles that can separate into single crystals called “fibrils” (Ross et al., 2008; Langer, 2008). The polyfilmentous bundles often display splayed ends where the fibrils are separating and flexible (Fig. 1). Owing to the bundles of fibrils, the monoclinic asbestos minerals have anomalous properties when x-rayed or rotated in polarized light (Campbell et al., 1977, 1980; Wylie, 1979; Ross et al., 2008; Langer, 2008). Non-asbestiform amphibole mineral particles are single crystals that do not display the flexibility found among the asbestiform minerals. Amphibole minerals can form with four different morphological appearances: massive, prismatic, finely acicular (or needle-like), and asbestiform (Dorling and Zussman, 1987; Kelse and Thompson, 1989, Fig. 1).

The nomenclature of the asbestos minerals is rather complex because the commercial names differ from the mineralogical names (Langer, 2008; Ross et al., 2008). Chrysotile is always an asbestos mineral and the mineralogical nomenclature uses this name. Crocidolite and amosite are commercial names specific for asbestiform riebeckite and asbestiform grunerite, respectively. The mineralogical nomenclature adopted by the International Mineralogical Association (IMA) does not recognize crocidolite and amosite as mineralogical names (Langer, 2008). Although “crocidolite” and “amosite” remain common in the medical and health effects literature, they are not used in the mineralogical literature (Hawthorne and Oberti, 2007). Currently, IMA has (2018–2022) formed a working group to re-evaluate mineralogical definitions of EMP, mineral fiber, fibril, cleavage fragment, fibrous, asbestiform, and asbestos (Wylie et al., 2022).

Exposure to asbestos is assessed by counting the airborne fiber with an aspect ratio of at least 3:1 and a length equal to or greater than 5 μm by phase-contrast optical microscopy at about 450× magnification. Although not counted in the exposure index, fibers shorter than 5 μm are still asbestos (Langer, 2008). Fiber length is not a defining criterion of asbestos.

The three asbestiform amphiboles other than crocidolite and amosite; *i.e.*, anthophyllite, tremolite, and actinolite (collectively referred to as “ATA”), were of markedly lesser

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commercial importance, and these amphibole names refer to both the asbestos and the non-asbestiform (massive) habit of these three amphibole minerals (Bank, 1980; Wilson et al., 2008). When they are asbestos, they are referred to as anthophyllite asbestos, tremolite asbestos, and actinolite asbestos. Mineralogists often refer to these minerals as asbestiform anthophyllite, asbestiform tremolite, and asbestiform ATA.

The focus of a 1992 rulemaking by the Occupational Safety and Health Administration (OSHA) was on EMPs of the non-asbestos ATA group and whether or not they should be regulated under the asbestos standard. Neither of the other two amphiboles with specific asbestos names, *i.e.*, crocidolite and amosite, were considered in the 1992 OSHA rulemaking process. Exposure to EMPs of the non-asbestos analogs of these minerals meeting the exposure index criteria also were not of sufficient concern to OSHA to be considered in the 1992 rulemaking process (OSHA, 1992).

There was limited production of anthophyllite-asbestos, mainly in Finland from 1918 until 1977 (Kiviluoto et al., 1979). Production of tremolite-asbestos and actinolite-asbestos was the least of all the six asbestos minerals.

OSHA and the Consumer Product Safety Commission have both reviewed the question of whether elongated cleavage fragments of actinolite, tremolite, and anthophyllite should be included in the asbestos standard, and both of these regulating organizations concluded they should not be considered asbestos or regulated as such (OSHA, 1992; Wilson et al., 2008; Crane, 2018). OSHA in this document considered the interface between mineralogical definition and health effects, citing one of us (BC) in his published contention that “The major flaw in the substitution of mineralogical definitions for microscopic characteristics is a reliance of the former on gross morphology. For regulatory and health assessment purposes, it is microscopical morphology that counts … “ (OSHA, 1992). The United States Environmental Protection Agency (US EPA) is currently considering expanding the regulatory definition of asbestos to include other minerals, in particular “Libby Amphibole Asbestos” and “asbestos-containing talc” (Wylie et al., 2022; US EPA, 2022).

Keeping these definitions in mind, the presentations in this session of the conference were aimed at summarizing what is known about asbestiform and non-asbestiform EMPs, and mesothelioma risks based on evidence from experimental and epidemiology studies.

2. Case reports

The starting point was a search of the scientific and other literature to find cases where mesothelioma had occurred and there was a postulated etiology involving a non-asbestiform EMP. In undertaking this task, Dr. Bruce Case brought to our attention that the very task that we were undertaking had already been set out in writing by Dr. Saracci at the International Agency for Research on Cancer (IARC) in 1980:

“Present-day knowledge, still limited in many ways, has tipped the balance from an *a priori* assumption of biological inertness of mineral fibres, natural and synthetic, to an assumption of biological, possibly pathological, activity; so much so that no fibre that can enter the body could nowadays escape close investigation in experimental systems as well as in exposed

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human groups. This holds true, in particular, for inhalable fibres of given geometrical characteristics, these being currently deemed as key determinants of fibre kinetics as well as fibre actions, including the carcinogenic one, at the tissue and cell level. A very wide ground for epidemiology investigation has thus been opened, whose exploration is only beginning" (Saracci, 1980).

Case reports can be divided into four eras: the first reported cases of either mesothelioma or one of its synonyms before the clear discovery of a relationship with exposure to EMPs in 1960–1965; the following twenty years of evolving assessment and evaluation of possible causes; a consolidation period of knowledge after 1980; and a predominance of litigation-associated case reports after approximately 2000. Like much of the medical literature, the latter have proliferated in recent years, with little new knowledge resulting.

Most case reports existed without reference to *any* exposure. Occupation may be mentioned as a surrogate for exposure without corresponding measurement and with varying rationale and suitability. Assumptions were sometimes made without actual evidence of the physical presence of the exposures in question, and often without full occupational and environmental histories being available. Early cases had two principal values: (1) as sentinel cases, and (2) as leading to other studies, not only epidemiology but, in the best instances, to details of causative exposure and mechanisms of disease production.

Case reports of mesothelioma after approximately 2000 have largely been produced in the context of asbestos litigation, compensation, or national asbestos amelioration programs. This affects the nature of the reports in four ways. First, these case reports are much more likely to have information on exposure(s) than are earlier case reports. Indeed, that may be the reason they were produced. Second, and related to the degree the cases themselves have information on exposure(s) or on surrogates for exposure(s) such as occupational status, they are subject to selection bias. Third, they are most likely reported by individuals or groups personally involved in the litigation, which introduces a source of (sometimes incorrectly) perceived conflict of interest. Fourth, and of greatest interest, such case reports found in the peer-reviewed literature have import for specific causation – including potential specific causation by non-asbestiform EMPs of a specific mineral.

The task of identifying reports where non-asbestiform EMPs were mentioned proved difficult. In fact, most case reports for mesothelioma (identified earlier by terms such as endothelioma) in the medical literature were published because of unique aspects of pathology, immunohistochemistry, molecular pathology/biology, treatment, and other clinical or basic medical science parameters. Etiology was not a major issue in most case reports, despite their often-cited potential sentinel value. They were largely uninformed by physical descriptions of suspect exposures, except for a few reports and case series having lung-retained fiber analyses.

A systematic search of PubMed, including "case reports" or similar terms for any form of mesothelioma or pleural or peritoneal cancer, identified 2660 published papers between 1900 and 2022 as of February 28, 2022. The term "asbestiform" occurred in only four publications, two of which referenced medicolegal talc cases in 2020. "Fibre" or "fiber"

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was mentioned in 18 papers, and “non-asbestiform” in none. In or after 1960, 292 papers contained the word “asbestos” in available texts. Many papers were missed, as case reports and especially case series did not and still do not necessarily use those terms. However, use of alternate search terms and other databases (US EPA HERO; SCOPUS) found even fewer relevant papers, while adding a few not in the PubMed search.

Expansion of search parameters to include any publication in the PubMed collection having the term “mesothelioma” produced slightly better results, in that 71 papers contained the word “asbestiform,” and 23 contained “non-asbestiform.” Of the latter, a small number were case series, but most were reviews or commentaries rather than case reports or analytical epidemiology studies. One exception for the latter was a very recent update of the Northern Italian talc miners and miller’s cohort, which found a lack of association between exposure to “talc with no detectable level of asbestos” and lung cancer or mesothelioma.

There have been some recent reviews of this subject. Minerals of chief interest in published reviews were talc, including talc “EMP,” as well as tremolite associated with talc. The latter can be asbestiform and in such cases is clearly associated with mesothelioma risk if exposure is sufficient. A “bright line” between asbestiform and non-asbestiform tremolite in some circumstances was hard to draw, a good example being the largely but not entirely non-asbestiform tremolite in and around the Quebec chrysotile mines, which is associated with a greater risk of mesothelioma (Case and Sébastien, 1989; Case et al., 2002).

Other minerals evaluated have been “non-asbestiform” and “asbestiform” ferro-actinolite and anthophyllite, the latter being difficult to distinguish in some instances. Non-asbestos minerals studied included fibrous zeolite (or erionite), fluoro-edenite, balangeroite associated with chrysotile, glaucophane, and other amphiboles associated with large-scale construction projects. There has also been literature (75 papers identified in PubMed for mesothelioma) on synthetic fibers (earlier referred to as ‘man-made mineral fibers’), which has led to a vacillating series of conclusions on possible carcinogenic potential, with a consensus negative conclusion. While some recent work is consistent with a possible synergistic effect with asbestiform fiber exposures, “effects of MMVF [Man-Made Vitreous Fibre] could not be disentangled from those of asbestos” (Pintos et al., 2009; Camiade et al., 2013).

Other than fibers, the most discussed mesothelioma cases in the “case report” literature were infection or general inflammation having other causes (especially in early work and strikingly neglected in recent work); radiation of various types, including both ionizing and nonionizing; and spontaneously occurring mesothelioma without clear environmental cause. The latter have been reviewed by Attanoos et al. (2018). Others included the SV40 virus, now largely debunked as a possible cause. Carbon nanotubes (CNTs), on the other hand, were found to be referenced in more “mesothelioma” papers (117) than were “asbestiform” fibers, due to the ability of a subset of needle-like, multi-walled carbon nanotubes (MWCNTs) to produce mesothelioma in animal models. Although disease in humans has not been reported, suggested mechanisms of disease production intriguingly recapitulate suggestions in both early case reports in mesothelioma (inflammation and its consequences) and more recent molecular and mineralogical correlates, including “fiber”

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dimensions. Human occupational exposure is being monitored in several countries, but the exposed population is inadequate to date for reliable inhalation exposure assessment.

3. Non-asbestiform epidemiology studies overview

Dr. Taioli took on the task of identifying epidemiology studies of non-asbestiform EMPs. She noted that while certain EMP exposures may be associated with mesothelioma (although not many, based on the review of cases by Dr. Case), one might speculate that the evidence has not been adequate to address the risk of populations exposed to non-asbestiform particles. She re-iterated the fact that because of the definition of an EMP by dimensions (*i.e.,* length >5 μm and aspect ratio of at least 3:1) and similarity to asbestos shape, they have been studied as possible risk factors for cancer, and specifically cancers of the respiratory tract and malignant mesothelioma. Dr. Taioli discussed the role of epidemiology in elucidating cancer risk in occupationally and environmentally exposed populations, noting the methodological issues related to both the assessment of outcome (mesothelioma) and of exposure. She informed us that, in general, mesothelioma is a rare cancer; therefore, most occupational studies are not powerful enough to detect meaningful associations because of the limited number of mesothelioma cases. She noted that registries where mesothelioma or other cancer cases are reported are also still very limited in number, and mostly created as a response to litigation or worker compensation efforts, rather than being population based. Several geographic areas worldwide have no specific mesothelioma registry, despite the known presence of asbestos. In terms of exposure measurements, most often, workers are exposed to a multitude of agents, and defining the amount and type of exposure even when using appropriate questionnaires is extremely difficult and often imprecise.

Dr. Taioli discussed the evidence published on talc, CNT, silicon carbide, erionite, sepiolite, palygorskite, and vitreous fibers and glass, as examples of compounds for which the overall assessment and consensus on human cancer risk was at different stages. For example, inhaled talc not containing asbestos or asbestiform fibers was considered by the IARC as not classifiable as to its carcinogenicity (Group 3) (IARC, 1987a, b). IARC classified a particular form of CNT (Mitsui-7) as ‘possibly carcinogenic to humans’ (Group 2 B) based on rodent data, but concluded it did not have sufficient data to classify other CNTs (‘not classifiable as to its carcinogenicity to humans’ (Group 3) (IARC, 2017; Grosse et al., 2014). IARC defined fibrous silicon carbide as possibly carcinogenic to humans (Group 2 B), while silicon carbide whiskers as probably carcinogenic to humans (Group 2 A). Erionite was classified as carcinogenic to humans in 2009 (Grosse et al., 2014). Possibly important in understanding the role of dimensions, Dr. Taioli noted that palygorskite long fibers were classified as possible carcinogens to humans, and short fibers were not classifiable (Group 3) (IARC, 1997).

Dr. Taioli informed us that the reason for the inconclusive evidence and uncertainty included the lack of precision and appropriateness of the measure of exposure; the lack of information on concomitant exposures; and the lack of proper statistical methods for addressing multiple exposures, study design, and adjustment for confounders. She found that a recent Medline search identified very little literature for these compounds, either in occupational or environmental settings.

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Dr. Taioli noted that novel approaches aimed at improving human studies included better definitions of exposure, details on the biological properties of EMPs, as well as impurities, surface area, and surface reactivity that could inform on the introduction of appropriate biological markers of exposure and effect, assessment of bias and measurement of confounders, routine introduction of biomarkers and other molecular measures in occupational settings, implementation of mesothelioma registries, and geospatial studies of cancer rates at county and zip code level. Of note was the lack of epidemiology studies, with most IARC evaluations based on experimental and limited human data. It became clear from Dr. Taioli's presentation that the epidemiology evidence concerning non-asbestiform EMPs was weak or lacking, and that progress would be limited unless registries were established as repositories for data that could be used for sound, well-designed epidemiology studies of rare cancers, such as mesothelioma (Cummings et al., 2019; van Gerwen et al., 2020).

4. Taconite miners

Dr. Taioli did not mention taconite in her talk, as it was considered to warrant specific attention. Taconite miners have been important in identifying the role, if any, of non-asbestiform particles in causing mesothelioma. Amosite is an asbestiform variety of the mineral grunerite. Taconite miners are exposed to grunerite, which is an amphibole with cleavages that allow for the formation of cleavage fragments. While an important follow-up of workers from that area is as yet incomplete, Drs. Mandel and Odo provided an update to 2022 of the situations in this mining sector.

Dr. Odo reported in his presentation that lower grade iron ore (taconite) mining has occurred in Minnesota and Michigan, following depletion of high-grade ore during the Second World War. The mining process consists of removing the ore from the Mesabi Iron Range and transporting it to processing centers, where the ore is uniformly crushed, separated, and concentrated. Although the amount of iron in the ore is consistent across the iron range, naturally occurring amphiboles occur exclusively in the eastern portion of the Mesabi Range. The predominant Mesabi Range EMP exposure currently is 1–3 μm in length and non-asbestiform in habit. Given the excessive mortality from mesothelioma in taconite miners, the issue of whether EMPs under 5 μm in length or shorter, thicker cleavage fragments contribute to the risk for mesothelioma is an important issue.

From the early 2000s until the present, the Minnesota Department of Health has identified an excess of mesotheliomas among the taconite mining cohort. Utilizing work history data from over 68,000 miners, identified by the University of Minnesota School of Public Health in the 1980s, standardized mortality ratios were determined for mesothelioma and found the ratio to be about three times higher than the State's comparison population. This is an unusual finding given that occupational assessments of talc and gold mining, with comparable non-asbestiform EMP exposures, have not demonstrated a clear-cut association of exposure with mesothelioma or any respiratory cancer (Gillam et al., 1976; McDonald et al., 1978; Selevan and Dement, 1979; Steenland and Brown, 1995; Honda et al., 2002; Wild et al., 2002; Coggiola et al., 2003; Pira et al., 2017; Wergeland et al., 2017; Ciocan et al., 2022). The Honda study had an elevated respiratory cancer standardized mortality ratio (SMR = 2.32, 95% CI = 1.57–3.29) that was not monotonic; only the taconite studies have

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shown a mesothelioma excess, but not lung cancer excess. Studies from these comparable exposure industries would suggest that taconite mining *per se* would not be expected to increase the risk for respiratory cancer and/or mesothelioma (Mandel et al., 2016).

Several studies of taconite mining have utilized a detailed exposure assessment process (Mandel et al., 2016; Mandel and Odo, 2018). Over 2000 current, on-site samples were originally collected by study investigators in 2010 and 2011 (Hwang et al., 2013). Samples included personal and area types for EMPs, silica, and respirable dust for each of 29 similar exposure job groups (SEGs) in six active mines. Silica and respirable dust are the most prevalent exposures in the industry and were gathered for that reason. Silica is an important consideration since it has known toxicity in the lung and has been implicated as a lung carcinogen. Area samples for EMPs included the use of a cascade impactor with size fractions ranging from 36 nm to 56 μm in length. These dimensions were measured by phase contrast and electron microscopy and counted using several dimension-based definitions of EMPs. Based on the use of the National Institute of Occupational Safety and Health (NIOSH) definition of EMPs, most onsite current measurements were within the recommended federal exposure limits. Measurements indicated that when excursions did occur, they were more likely to be in the eastern part (Zone 4) of the Mesabi Range (Fig. 1). The east range measurements also identified non-asbestiform amphibole EMPs, which were not present on the west range. There were no asbestiform EMPs identified in any of the samples, defined by NIOSH as silicate minerals from the serpentine and amphibole groups that grow in a fibrous habit. Although detected in the east, the current, on-site non-asbestiform amphibole EMP measurements were typically a magnitude or more below the NIOSH Recommended Exposure Limit (REL).

Historical EMP measurements (n = 682) were identified from two sources: (a) the Mine Data Retrieval System maintained by the Mine Safety and Health Administration (MSHA), and (b) the internal industrial hygiene monitoring databases of US Steel and Cliffs Natural Resources, two of the currently operating taconite mining companies. By combining comprehensive on-site exposure concentrations with the relatively fewer historical data, exposure concentration matrices were developed that were used to estimate cumulative exposures for individual workers. Using the measured data and regression model estimates, exposures were reconstructed for each SEG for each mine and for each year between 1955 and 2010 for all three exposure types. Based on these estimates, EMP exposures were likely to have been higher in the earlier days of the industry. These exposure estimates were then used in the additional studies.

A previous case-control study of taconite workers assessed the risk for mesothelioma among 80 cases and 320 controls (Lambert et al., 2016). In Lambert et al. (2016), EMPs were identified by phase contrast microscopy, and were defined as being over 5 μm in length with a 3:1 aspect ratio. Cumulative exposure was determined from an extensive on-site exposure assessment of all SEGs in all active mines (above). High (*vs.* low) cumulative exposure to EMPs was determined to be associated with a risk for mesothelioma [Rate Ratio (RR) = 2.25, 95% CI = 1.13–4.5]. The unit RR in this study (risk for one year of follow-up) was 1.03 (95% CI = 1.0–1.06). Comparisons were made of workers in the eastern iron range to

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the west. Despite the presence of amphibole EMPs in the east, the risk for mesothelioma was not elevated for miners who worked in this geographic location.

There were several limitations of the Lambert investigation. Most importantly, historical exposure estimates to EMPs were sparse. Secondly, one plant, where around 50% of the mesothelioma cases worked (Zone 2 of above map), closed in 2000 and historical samples were largely not available due to missing records. Thirdly, smaller EMPs (less than 5 μm in length) were not assessed in this study. Fourth, an attempt was made to control for the likelihood of exposure to commercial asbestos in standardized job categories. Although this was done, sizable numbers of work history records were incomplete. As a result, cumulative exposure was not necessarily accurately tied to specific standardized jobs (SEGs). Dr. Odo in his talk mentioned the important fact that although the Minnesota Department of Health Cancer Surveillance System (MCSS) uses tumor data based on a pathological report, many of these cases have been diagnosed from clinical presentation, sometimes without histological confirmation and often without autopsies performed. Clearly, this is an important issue that needs to be addressed in any follow-up.

In summary, although studies of taconite miners in Minnesota have demonstrated an excess of mesothelioma, it remains uncertain as to the role of non-asbestiform EMPs in this finding. Studying this role has been complicated by an incomplete understanding of historical asbestiform exposures and lack of assessment of fibers less than 5 μm in length. Studies are currently underway to address the latter issue.

5. National Mesothelioma Virtual Bank (NMVB)

Dr. Becich introduced the audience to the existence in the US of a rather unique tissue bank for mesothelioma tissues. He also provided an example of the value of a registry such as this for epidemiology studies. As mentioned by Dr. Taioli in her presentation, another approach to identifying key areas for research and the potential for EMP risks is looking at where mesotheliomas occur and obtaining information about exposures from mesothelioma cases. Some early studies were conducted using both cases and controls in North America by Drs. Corbett and Alison McDonald and colleagues in the 1970s. These studies identified links between exposure in shipyards and certain industrial processes and mesothelioma. Recently, a similar approach was used to see what occupations were potentially linked to mesothelioma.

The National Mesothelioma Virtual Bank (NMVB) (Amin et al., 2008, 2013, 2018) is a virtual mesothelioma patient registry that includes mesothelioma patients' lifetime work history, exposure history, and biospecimens/proteogenomic/imaging data (Hmeljak et al., 2018; Karunakaran et al., 2021) and currently contains over 2000 patients. Data for the registry are currently contributed by seven academic health centers, including New York University, University of Pennsylvania, University of Pittsburgh Medical Center, Mount Sinai School of Medicine, Roswell Park Cancer Institute, University of Maryland, and Baylor College of Medicine, and is expanding to Fox Chase Cancer Center and Temple University. To examine the industry and occupation of mesothelioma patients, they mapped NMVB's free-text work information collected from patients diagnosed with malignant

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mesothelioma during 2006–2020 to standard industry and occupation codes using the NIOSH Industry and Occupation Computerized Coding System. Of 1444 mesothelioma patients, 781 (54.1%) had information on industry and occupation. Among those with available demographic data, 96.1% (635/661) were aged >40 years at the time of diagnosis (median age at the time of diagnosis was 67 years), 79.7% (613/769) were males, 96.9% (717/740) were White, and 97.3% (693/712) were non-Hispanic. Of 1126 recorded industries (up to 6 industries could be recorded for each patient), the most frequently recorded industries were construction (No = 161, 20.6%), iron and steel mills and steel product manufacturing (No = 62, 7.9%), and the US Navy (No = 45, 5.8%). Of 980 recorded occupations (up to 7 occupations could be recorded for each patient), the most frequently recorded occupations were military (No = 60, 7.7%), construction laborers (No = 54, 6.9%), and production workers (No =32, 4.1%). Patients aged >40 years at the time of diagnosis tended to have worked in industries traditionally associated with mesothelioma (*e.g.*, construction), while patients aged 20–40 years (No = 26) tended to have worked in industries not traditionally associated with mesothelioma (*e.g.*, justice, public order, and safety activities) (Table 2). Among patients that reported exposure to asbestos at work for greater than 6 months (No = 485, 62.1%), the most frequently recorded industries were construction (reported by 73 patients), iron and steel mills and steel product manufacturing (No = 34), and the US Navy (No = 29), while the most frequently recorded occupations were military (reported by 49 patients), construction laborers (No = 37), and electricians (No = 24). The NMVB patient registry has the potential of serving as a sentinel surveillance for identifying industries and occupations not previously associated with mesothelioma. To accomplish this goal, the NMVB is planning to link its data repository to two databases of lung sample digests examining amphibole fibers from patients who have confirmed histologic diagnoses of mesothelioma by pulmonary pathology specialists. NMVB will also strive to expand collaborative linkages with other US (Cummings et al., 2019) and international registries (van Gerwen et al., 2020).

6. EMP dimensions and biopersistence

Dr. Bernstein informed us that there is a strong consensus that long, highly durable respirable EMPs have potential to cause mesothelioma; however, there is continued debate concerning the biodurability required, the dimensions (both length and diameter), the shape, and the dose associated with mesothelioma. In his presentation, he focused mainly on the particles derived from non-asbestiform amphiboles.

Dr. Bernstein noted that cleavage fragments are clearly different from EMPs that are amphibole asbestiform fibers in key parameters that are known to influence an EMPs potential to cause harm. These include their formation and shape, their respirability, their interaction with the lung’s physiology, and clearance from the lung. He emphasized that cleavage fragments could be formed when amphibole-containing rock is crushed. In this instance, fragments are shaped by two directions of perfect cleavage parallel to the c-axis and, as a result, are elongate (Wylie, 2016; Belluso et al., 2017). The result is that they are often irregular in shape, and while they may have aspect ratios of greater than 3:1, they are usually shorter than 10 μm in length and may be thicker at one end. This contrasts with amphibole asbestiform fibers, such as crocidolite and amosite, which are usually symmetric

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and cylindrical in shape with a large distribution of lengths often exceeding 50–100 μm. The diameter of the asbestos fibers at one end is similar to that at the other end. Amphiboles have good prismatic cleavage in all habits other than asbestiform; they all will break into acicular fragments, and most will satisfy the 3:1 aspect ratio (Zoltai, 1979).

Through a series of images of cleavage fragments and asbestos fibers, together with information on structural strength, surface defects, and other parameters, Dr. Bernstein illustrated why cleavage fragments based on their dimensions alone would not be expected to have the same effects as asbestos fibers. However, he noted that while the concentrations of particles in air have been reported in several industrial circumstances and in experimental systems, the airborne exposures specifically to non-asbestiform EMPs is lacking.

Dr. Bernstein noted that as far as respirability is concerned, for most fibrous silicates, a width of about 3.5 μm approaches the limit of respirability (Timbrell, 1965), and airborne cleavage fragments are often of this size. However, the primary factor determining whether a fiber can deposit in the lung is the aerodynamic diameter. For short fibers, which would include most cleavage fragments, the fiber length would have a minor influence on the aerodynamic diameter, with the density being the most significant determinant. Once inhaled, the longer the fiber, the more likely it is to align with the airstream, which would facilitate long, thin asbestiform fibers penetrating into the lung parenchyma. However, thicker shorter fibers like cleavage fragments would be more likely to have random orientations and based on aerodynamics likely result in less deposition in the deep lung. Dr. Bernstein postulated that with commercial amphibole asbestos use, exposure would be to a relative pure fiber atmosphere; whereas, crushing rock from a non-asbestiform amphibole would produce a lower concentration of respirable particles and it would be unlikely that exposure levels would ever approach those resulting from a non-asbestiform amphibole exposure.

As noted earlier, not only are dimensions important for inhalation, deposition, and particle removal, but biopersistence is also crucial. Indeed, while a key parameter, there are no *in vivo* biopersistence studies of either cleavage fragments or short fibers of amphibole asbestos. Dr. Bernstein asserted that amphibole particles/fibers will not readily dissolve in the lung at either neutral or acid pH. Further, there have been no inhalation studies to determine whether cleavage fragments can break apart or cleave in the lung once inhaled, but it appears unlikely that there will be significant breakage given the nature of the material. As cleavage fragments have been shown to be short and nearly all <10 μm in length, their clearance can be considered similar to that of short fibers and such particles would likely clear at rates similar to insoluble dust, which are considered innocuous.

Dr. Bernstein noted that the clearance of cleavage fragments, where there are no long amphibole asbestos fibers present, would be different from the clearance of a mixed amphibole asbestos aerosol of short and long fibers. With amphibole asbestos aerosols that contain fibers longer than ~20 μm, Bernstein et al. (2021) has shown, using confocal imaging, that the intense inflammation caused by the long fibers, once inhaled, quickly locks up the shorter fibers that may deposit in the same regions. In those regions of the lung without such long fiber-initiated inflammation, short fibers have not been observed to accumulate. This combined with what would be present in the lymphatic system and nodes would result in many short fibers remaining in the lung.

It seems that if long, thin asbestiform fibers are released in conjunction with amphibole cleavage fragments, such aerosols should be evaluated for the exposure concentration of the long fibers and their dose response.

7. High Aspect Ratio Engineered Nanomaterials

As noted above, there is increasing use of nanoparticles in society, including CNT and carbon nanofibers. Dr. Nel described what can be learned from the experimental study of these nanomaterials. He noted that the fiber pathogenicity paradigm (FPP) was developed in the 20th Century to explain the pathway of injury of natural and synthetic fibers for elongate particulates in the lung, including carcinogenic potential and ability to generate mesotheliomas. Much of the discovery leading to the construction of the FPP was based on elaborate data gathering on heterogeneous EMP populations, leading to the identification of EMP dimensions (length/width), biopersistence, and surface reactivity as important features determining whether the fibrous or elongate materials are respirable, can be deposited in the deep lung beyond the mucociliary region, retained, and allowing access to the pleural space. The parietal pleura constitutes the key retention site for long biopersistent fibers, capable of obstructing and damaging the parietal pleura pores. This leads to chronic inflammation and initiation of a march of events that may culminate in malignant transformation. However, despite the progress made for asbestos fibers, there is an ongoing need to refine the exact length, width, and biopersistence characteristics of a large range of other EMPs and synthetic fibers not characterized in terms of their structure-activity relationships that could lead to lung injury.

The ability to exert more exact control over the length and biopersistence of high aspect ratio (HAR) engineered nanomaterials has recently made valuable contributions to understanding and confirming the tenets of the FPP. This includes data generation with libraries of CNT and metal nanowires, which have helped to establish critical length dimensions required for obstructing pleural stomata, interference in lymphatic drainage, and generation of acute and chronic mesothelial inflammation (Murphy et al., 2011). The findings include evidence for the ability of long and rigid, but not short and flexible, multi-wall CNTs to induce mesothelioma in experimental animals, subjected to installation or whole body inhalation exposure. The rodent experimentation has helped to clarify the structure-activity relationships that are involved in the carcinogenic response to rigid, needle-like multi-wall CNTs, as compared to other types of CNTs.

Considering the existing experimental evidence for EMPs, including materials of mineral or non-mineral composition, Dr. Nel's presentation provided an explanation of the structure-activity relationships involved in the pathogenic effect of HAR nanomaterials in the lung, including being able to distinguish between adverse outcome pathways that promote carcinogenic *vs.* pro-fibrotic effects in the lung (Nel, 2022). In particular, long and rigid, multi-wall CNTs could be seen to induce frustrated phagocytosis, with the capability of gaining access to the pleural cavity and ability to generate mesotheliomas, while shorter

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and flexible multi-wall tubes or single-wall CNTs are not equipotent. However, some of the materials in the latter categories could induce lung fibrosis based on the ability to induce epithelial mesenchymal transition. These animal data are also compatible with the classification of the long, rigid Mitsui-7 multi-wall CNT as possibly carcinogenic (Group 2 B) agent, while also commenting on the lack of sufficient data for classifying other CNTs (Group 3). In addition to CNTs, it was possible to use the exact length dimensions of silver and nickel nanowires to demonstrate exact length thresholds for inducing acute and chronic mesothelial inflammation, confirming that a length of approximately 5 μm and longer, is critical for obstructing stomata in the parietal pleura. These data are in accordance with the historical length estimation for potentially hazardous EMPs, as originally envisaged by the FPP.

In addition to the clarification of dimensional and durability features, experimentation on CNTs has also shed new light on the impact inflammation and oxidative stress on epigenetic regulation of tumor suppressor genes and the generation of immune suppressive effects at the mesothelioma tumor microenvironment, which is helpful for understanding tumor development and the possibility of new therapeutic approaches for this difficult to treat malignancy (Nel, 2022).

8. Future research

The reviewers of both case reports and epidemiology drew attention to the lack of clear descriptions of the exposures to non-asbestiform EMPs both qualitatively and quantitatively. Further, there has been little attention paid to contaminants and impurities of exploited minerals. There was also a clear expression of the need for improved registries and quality of data that they might collect.

As far as the taconite mines are concerned, Drs. Mandel and Odo offered suggestions for the future. They noted that in such studies it will be important to evaluate the predominant EMP exposure in this industry, that being from shorter (under 5 μm), non-asbestiform, types. An updated case-control study is in progress and was specifically designed to clarify mesothelioma risk for shorter EMPs and cleavage fragments. This has incorporated an additional 24 cases and 96 controls from the original Minnesota taconite cohort, *via* the Minnesota Department of Health. Samples that were taken as part of the Hwang exposure assessment in 2013 were used with electron micrographic techniques (TEM, ISO 10312/13,794) to count EMP dimensionally. A mathematical approach has been developed to derive conversion factors between the different EMPs, define these factors dimensionally, and apply them to previously described job exposure groupings. This allows for the creation of a job exposure matrix based on exposures from different sized EMPs (Shao et al., 2020). However, as with the Lambert study, exposure to commercial asbestos and the lack of records from one inactive plant where a disproportionate number of cases occurred are still potential problems. They also noted that the update to the case-control study is currently in progress.

On the experimental side there is little known quantitatively about the biopersistence of non-asbestiform EMPs or the influence of mixed asbestiform and non-asbestiform particles on

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particle clearance from the lung. Little was also said concerning the likelihood of cleavage fragments reaching the pleura. It will be important to acquire these materials for purification to conduct experimental studies.

While the HAR nanomaterial exposure-generating industries are in their infancy, the likelihood of having a clear answer concerning links with mesothelioma because of latency is low. The undertaking of occupational exposure studies in the CNT industry, with the aim of linking exposure dose to biomarkers and health effects outcomes, is of critical importance to ongoing risk assessment. The ongoing surveillance of mesothelioma through registries combined with well-documented exposure data could contribute in an important way to determining whether the nanocarbon fibers or similar fibers are causing mesothelioma in humans. The development of 21st-century toxicological approaches that were used for conducting CNT hazard and safety assessment (e.g., adverse outcome pathways and integrative assessment and testing approaches), should also be of value for toxicological modeling of asbestos and other EMP materials.

Finally, while the evidence to date points to the likelihood that there are few if any non-asbestiform EMPs posing a risk of mesothelioma, there is clearly a need for a systematic study of the exposures of people with mesothelioma and comparison to appropriate controls to ensure that this is the case. Such a study could build on the work already undertaken in establishing the virtual mesothelioma tumor registry and on studies of lung tissue from litigation cases and also from case-control studies of mesothelioma undertaken in the United Kingdom. Past studies have concentrated on asbestos; future studies need to be broader and include other minerals and other particles and dimensions. Such studies would need to apply methodologies that do not alter the dimensions or composition of any EMPs found in lung tissue at death. Further, the association with specific minerals or other particles would require comparison of the lung tissue content of persons with mesothelioma with the lung content of appropriately matched controls gathered from across the US or other countries in which such studies might be conducted. To do this, it is suggested that a prospective study in which lung tissues, mesothelioma tissues, and control lung tissues are collected over 2–3 years be initiated in which the precise location of lung tissue samples and collection methodology is stringently controlled. This would be accompanied by detailed work histories, as discussed in this conference. Such histories should also include environmental, hobby, and family contact exposures. Lung tissue analyses would only be undertaken at qualified laboratories after all techniques have been thoroughly evaluated and precise methodology established. Tissues would be examined for content, particle composition, and particle dimensions. Such a study would establish which, if any, elongate particles other than asbestos are associated with mesothelioma and which are not, so that regulations can be appropriately focused and public concern about living or working close to sources of EMPs (*e.g.*, arising from quarries and roads not associated with mesothelioma) would be allayed as is scientifically appropriate.

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"Analysis of self-reported work history of mesothelioma patients in the National Mesothelioma Virtual Bank," which is a full-length manuscript in *Environmental Research* accompanying this Monticello II Workshop Summary.

Data availability

No data was used for the research described in the article.

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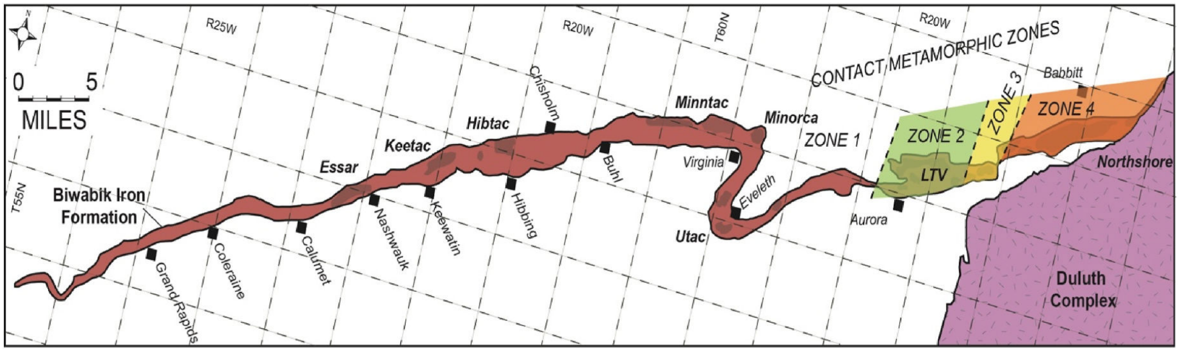

Fig. 1.

Mesabi iron range. (McSwiggen and Morey, 2008; Monson Geerts et al., 2019)

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Table 1

The six regulated asbestos minerals, including their elemental compositions and crystal systems. The Chemical Abstract Service Numbers (CAS Nos.) are included because the asbestos minerals and their rock forming analogs are recognized as being different and each is given a unique CAS No.

Serpentine Group	**Asbestiform Variety – CAS No.**	**Non-Asbestiform Variety – CAS No.**
$Mg_3(Si_2O_5)\ (OH)_4$	Chrysotile – 12,001–29-5 (Monoclinic)	Antigorite – 12,135–86-3 (Monoclinic) Lizardite – 12,161–84-1 (Trigonal)
Amphibole Group	**Asbestiform Variety – CAS No.**	**Non-Asbestiform Variety – CAS No.**
Monoclinic Crystal Sstem		
$Na_2(Fe_3^{2+}, Fe_2^{3+})\ (Si_8O_{22})\ (OH)_2$	Crocidolite – 12,001–28-4 (Riebeckite-Asbestos)	Riebeckite – 17,787–87-0
$Fe_7^{2+}(Si_8O_{22})\ (OH)_2$	Amosite – 12,172–73-5 (Grunerite-Asbestos)†	Grunerite – 14,567–61-4
$Ca_2Mg_{5-4.5}Fe_{0.0-0.5}\ (Si_8O_{22})\ (OH)_2$	Tremolite-Asbestos – 77,53668–6	Tremolite – 14,567–73-8
$Ca_2Mg_{5-4.5}Fe_{0.5-2.5}\ (Si_8O_{22})\ (OH)_2$	Actinolite-Asbestos – 77,53666–4	Actinolite – 68,992–52-9
Orthorhombic Crystal System		
$Mg_7(Si_8O_{22})\ (OH)_2$	Anthophyllite-Asbestos – 77,536–67-5	Anthophyllite – 17,06878–9

Note:

†Cummingtonite is the magnesium-rich end of the grunerite-cummingtonite solid solution series, which has specific CAS Nos. For asbestos (1332–21-4) and non-asbestiform varieties (17499–08-0).

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Table 2

Top ten industries for national mesothelioma virtual bank patients by age.

21–30	**#**	**31–40**	**#**
Health Care and Social Assistance	4	Health Care and Social Assistance	5
Educational Services	2	Manufacturing	4
Accommodation and Food Services	1	Educational Services	3
Finance and Insurance	1	Public Administration	2
Other Services (except Public Administration)	1	Military	2
		Mining, Quarrying, and Oil and Gas Extraction	1
		Accommodation and Food Services	1
		Agriculture, Forestry, Fishing and Hunting	1
		Finance and Insurance	1
		Information	1
41–50	#	**51–60**	#
Health Care and Social Assistance	12	Manufacturing	32
Manufacturing	10	Construction	20
Retail Trade	10	Other Services (except Public Administration)	16
Other Services (except Public Administration)	7	Professional, Scientific, and Technical Services	15
Transportation and Warehousing	5	Educational Services	11
Construction	5	Health Care and Social Assistance	11
Accommodation and Food Services	4	Retail Trade	10
Professional, Scientific, and Technical Services	3	Public Administration	10
Educational Services	3	Transportation and Warehousing	8
Finance and Insurance	3	Administrative and Support and Waste Management and Remediation Services	6
61–70	#	**71–80**	#
Manufacturing	77	Manufacturing	71
Construction	45	Construction	47
Military	30	Transportation and Warehousing	19
Health Care and Social Assistance	24	Educational Services	18
Educational Services	23	Public Administration	15
Public Administration	21	Military	13
Retail Trade	20	Professional, Scientific, and Technical Services	12
Professional, Scientific, and Technical Services	20	Other Services (except Public Administration)	10
Other Services (except Public Administration)	18	Finance and Insurance	7
Transportation and Warehousing	15	Health Care and Social Assistance	7
81–90	#	**91 +**	#
Manufacturing	18	Educational Services	1
Construction	11	Information	1

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21–30	#	31–40	#
Military	7	Professional, Scientific, and Technical Services	1
Professional, Scientific, and Technical Services	5	Transportation and Warehousing	1
Educational Services	3		
Administrative and Support and Waste Management and Remediation Services	2		
Transportation and Warehousing	2		
Other Services (except Public Administration)	2		
Mining, Quarrying, and Oil and	2		
Gas Extraction			
Public Administration	2		