ASBESTOS EXPOSURE: HOW RISKY IS IT?

A position paper of the American Council on Science and Health

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Executive Summary

The hazard, exposure, and risks associated with asbestos fibers have been explored and debated for many years. Human evidence suggests an association between exposure to asbestos and asbestosis, lung cancer, and mesothelioma, although the lack of consistent information on fiber type, size, and exposure concentrations and duration limit our ability to establish causal relationships between exposure and disease in some cases. While uncertainties remain in our ability to consistently and accurately quantify asbestos risk to humans, progress has been made in characterizing those key factors, namely hazard and exposure, that are critical to an assessment of health risk.

Because asbestos is a natural material, there will always be some background or ambient exposure to humans. Although mining and commercial applications have diminished in some parts of the world, asbestos continues to have commercial applications, and hence, there remains exposure potential from these sources. Chrysotile and amphibole asbestos are the types most commonly used and hence studied experimentally, and it has become increasingly clear that they differ with respect to toxicity and disease potential. This has been demonstrated in animal models, which appear to be reflective of the human situation as well.

Progress on a number of fronts has led to general scientific consensus on the following: (1) amphibole fibers (which tend to be relatively long and thin) are a more potent risk factor for the development of mesothelioma and, to a lesser degree, lung cancer than are chrysotile fibers (which tend to be relatively short and wide); (2) longer, thin fibers are more pathogenic and there appear to be fiber size thresholds below which asbestos fibers do not pose any threat; and (3) those animal studies in which high exposure concentrations resulted in lung overloading are not considered relevant to humans.

Analysis of the epidemiological literature supports some common patterns including: (1) for occupational and industrial exposures, the weight of evidence does not consistently support causal relationships between asbestos exposure and onset of pulmonary disease, some studies showing associative relationships but others showing no relationship between exposure and disease onset; and (2) chrysotile alone, uncontaminated by other fiber types, particularly amphiboles, does not appear to be a risk factor for mesothelioma, as once thought.

Advances in risk assessment methodology and analytical techniques, together with reevaluation of historical data, reveal that the current Environmental Protection Agency (EPA) approach for risk assessment of asbestosis is not in step with current scientific consensus, particularly for chrysotile fibers. In recent years, new knowledge about how asbestos risk can be more accurately and quantitatively determined has been generated. There is thus a scientific basis for adoption of these methods by regulatory agencies, including the EPA. While occupational exposures to asbestos remain and should be vigi-
lantly monitored, there appears to be no compelling scientific evidence that ambient exposure to chrysotile asbestos poses a significant health risk.

I. Introduction/Background

The Issue
While there are compelling data that support a causal relationship between asbestos exposure and human disease, particularly for historical occupational exposures, debate remains relative to the degree of risk from current ambient exposures. Asbestos is not a typical hazard for which known toxicological mechanisms and exposure-response relationships have been defined with complete certainty, in part because of the variables that influence an accurate determination of risk, including exposure level and duration, fiber type and size, and type of disease. These difficulties notwithstanding, substantial progress has been made over the past 25 years in our knowledge on these same points and how they influence risk to humans. The challenge today is whether regulatory agencies will utilize current scientific knowledge even though it will necessitate a paradigm shift in long-held views on asbestos exposure and its implications for human health.

Asbestos Defined
The term asbestos refers to a group of naturally occurring (asbestos is mined, not synthesized) magnesium and calcium silicate minerals. Asbestos exists in nature as both asbestiform (fibrous) and nonasbestiform (massive or amphibole) structures. The primary types with commercial application are chrysotile (the most common serpentine form of asbestos), and crocidolite and amosite (both of which are amphibole forms of asbestos). There are other amphibole forms, but they are either rare or their commercial use has been discontinued.

Sources of Asbestos
Asbestos is widely distributed in the Earth’s crust, and chrysotile, which accounts for more than 95% of global mining and use, occurs in virtually all serpentine minerals (Chrysotile Institute, 2006). Asbestos deposits have served as commercial sources in more than 40 countries, but the largest natural deposits are located in Canada, South Africa, China, and Russia (Niklinski et al., 2004; Chrysotile Institute, 2006). Over 99% of asbestos used in the United States is chrysotile, and the major chrysotile mines are located in Canada, Italy, Cyprus, and Corsica (Niklinski et al., 2004). Amosite and crocidolite have been mined from South Africa, while crocidolite was also once mined in Western Australia.

Uses
Asbestos has had important (often life-saving) commercial applications such as fireproofing and insulating materials. By the mid-twentieth century, asbestos, due to its unique properties, was widely used as a component of automotive brake linings, as pipe
insulation, as an additive for floor tiles in buildings, as insulation and fireproofing in warships, and in electrical distribution systems. By 1997, asbestos use in the U.S. was 6% of what it was in 1980, the decline generally ascribed to concern over health risks. A breakdown of the 1997 data showed that 48% of domestic consumption was for roofing products, 29% was for friction products (automotive uses), and 17% was for packing and gaskets (ATSDR, 2001).

**Asbestos and Disease**

Inhalation of asbestos particles (fibers) has been linked to pulmonary disease including asbestosis, lung cancer, and mesothelioma. However, confusion and debate remain about which type(s) of asbestos pose a risk, the degree of risk, and under what conditions of exposure these risks occur. Clearly, part of the difficulty in establishing defined exposure-response relationships for asbestos arises from the fact that asbestos is a generic term used to describe a number of fibrous minerals with differing toxicological properties and propensities for causing disease.

Both human and animal studies provide insight into the relationship between exposure to asbestos and disease or toxicity. Laboratory animal studies are conducted to understand basic dose-response relationships between exposure and toxicological effects. Differentiating between fiber types used in animal studies and those monitored in human studies is critical, something which historically has not been easy to determine accurately. Additionally, animal inhalation studies frequently employ high concentrations in order to characterize the dose-response range and to identify frank toxicological effects, concentrations which ultimately may not be relevant to human exposures. Thus, animal studies, while useful in hazard identification, may be inappropriate for human risk assessment.

Epidemiological studies (i.e., the study of the distribution and determination of diseases in humans) are conducted to establish association between the incidence of certain diseases and possible exposures to agents. The asbestos database consists of more than 150 such studies. While impressive in number, many of the studies are of limited value for evaluation of risk, due to lack of information on (1) fiber types, (2) measures of human exposure, and (3) confounding factors such as smoking. In addition, some studies were performed with mixed fiber types, in which specific fiber type was not determined or reported. Recognition of these limitations does not imply that the animal and human studies are not useful or informative but that they diminish our ability to rely exclusively and confidently on these when assessing risk to humans. A primary focus today when assessing the utility of human studies should be determining whether fiber type was analytically characterized and whether accurate exposure monitoring (i.e., personal monitoring) was conducted.
Advances in Knowledge

Despite the relative shortcomings of the historical database for asbestos, there have been recent advances which should be considered in regulatory, clinical, and legal forums. These advances include 1) insight and knowledge on the relative potency of specific fiber types; (2) insight on lung overloading in animal models and its implications for humans, and (3) progress in human health risk assessment approaches. Despite this progress, the EPA continues to rely on outdated guidance for evaluation of asbestos-related exposures and risks (EPA, 1986). Given advancements in our knowledge, there is a compelling scientific basis for revisions to this risk approach which has important implications for public health and general societal awareness and education on asbestos and risk.

Present-Day Concerns

For an occupational hazard that has been studied as extensively as has asbestos, uncertainty still remains about the exposure-specific concentrations of asbestos that might pose a risk to humans. It is generally recognized that in many regions of the world today, the asbestos form most causally linked to cancer (i.e., amphibole) is not commonly used in industrial settings or for commercial applications (Bartrip, 2004). More than 99% of the asbestos used in the United States is chrysotile asbestos (ATSDR, 2001). Improved engineering controls, employment of personal protective equipment (e.g., respirators, dust masks, HEPA filters), and industrial hygiene practices have greatly reduced occupational exposures to a number of respiratory hazards, including asbestos.

As such, the public health basis for continued attention to human asbestos exposures, particularly those involving ambient or background exposures, has diminished. Public health focus should remain on individuals whose exposure to certain asbestos fiber types remains above acceptable levels or for durations of long exposure. Efforts should also be directed at education and protection of individuals involved in large-scale asbestos remediation efforts, scenarios that may involve substantial exposure. Research efforts should clarify whether chrysotile asbestos is devoid of carcinogenic potential, particularly at current levels of exposure to humans, as current evidence increasingly suggests. Finally, lessons learned from the intensive study of asbestos can and should be extended to other fibrous materials, so that knowledge gained with asbestos can be leveraged for the benefit of all public health.

II. Asbestos - Physical Characterization and Relationship to Hazard Potential

The chrysotile and amphibole types of asbestos can be distinguished by their individual characteristics. In nature, chrysotile is a sheet silicate that folds or rolls into tiny tubular structures possessing a hollow core, whereas amphiboles are chain structures (Bernstein, 2005). Because of its unique physical structure, chrysotile, when processed either during milling or other mechanical disruption, tends to break down to produce separate fibrils
(long, thin, flexible particles that resemble scrolls or cylinders). The chemical composition of the amphibole fibers is complex since the silicate framework that makes up the amphibole structure may include a mixture of different ions (Bernstein and Hoskins, 2006). The external portion of the crystal structures of the amphiboles is quartz-like, including similar durability and chemical resistance, likely factors in their enhanced potency relative to pulmonary disease. Amphibole fibers tend to be straight and splinter-like if they are mechanically disrupted or disaggregated (Bernstein and Hoskins, 2006).

A characteristic that contributes to the relative respiratory hazard of different fiber types is biopersistence, that is, the degree to which fibers remain or persist in the body. Biopersistence is influenced by fiber size which in turn dictates respirability, deposition, and clearance from the lung. Chrysotile, when compared to numerous mineral fibers, has appreciably greater solubility and less biopersistence, whereas amphiboles are considerably more persistent and, hence, have a greater potential for carcinogenicity (i.e., mesothelioma). Chrysotile has been shown to be rapidly removed from the lung following inhalation exposure in experimental animals (Bernstein et al., 2005), while lung analyses from humans (Albin et al., 1994) who were primarily exposed to chrysotile fibers show low levels of chrysotile compared to amphibole fibers even when amphibole exposure represented a trace impurity of overall exposure (Rowlands et al., 1992).

There appears to be growing scientific support for the view that the epidemiological literature and mechanistic animal studies show a strong correlation between fiber length and carcinogenic potency for asbestos (ATSDR, 2001). This has implications in causation analysis, as well as for risk assessment, in which it is scientifically justified to give greater importance to fibers greater than 10 µm in length. Fiber diameter is also an important determinant of carcinogenic potency, as it influences fibers’ aerodynamic diameter — a contributing factor for pulmonary deposition. Specifically, the diameter of fibers impacts their dissolution rate (removal from the body) and thus the amount of time they have to interact with biological systems. The prevailing consensus is that carcinogenic potential depends upon both fiber length and diameter, with fibers greater than 10 µm in length and smaller than 0.50 µm in diameter generally considered to possess enhanced carcinogenic potential. Short fibers (i.e., 2-3 µm) and those whose diameters exceed approximately 1.5 µm have not been shown to possess similar carcinogenic potential.

The following general conclusions can be made about particle respirability (EPA, 2003):

- Fibers that are deposited in the lung are usually thinner than approximately 0.7 µm and are almost always thinner than 1 µm.
- Long, thin fibers are deposited in the lung with greater efficiency.
- Because of physical/chemical differences, short, thick chrysotile structures will be deposited more efficiently in the lung than corresponding (i.e., short, thick) amphibole structures and longer, thinner amphibole structures are typically deposited more efficiently than corresponding chrysotile structures.
• Curly chrysotile structures are less likely to reach the lung than are straight amphibole (or chrysotile) structures.
• Most fibers, regardless of size, are deposited with greater efficiency in rat lungs than in human lungs, owing to anatomical differences in respiratory structures.
• Because of anatomical differences between rats and humans, rats typically accumulate fiber burdens at a rate that is several times that of humans, assuming exposure to equivalent airborne concentration; therefore, studies in which lung overloading occurs in rats need to be carefully evaluated for relevance to humans.

Implications
There are significant physical, biopersistent, and toxicological differences among different types of asbestos fibers, which have implications for the intrinsic hazard they possess relative to human exposure, pulmonary clearance, and disease potential. There is general scientific consensus that chrysotile is more readily cleared from the body than amphibole forms. Longer, thinner fibers are more biopersistent than shorter, thicker fibers. Ultimately, these physical/chemical and toxicological differences increasingly appear to be important determinants in potential pathogenicity for human disease.

III. Asbestos Toxicity

Animal Evidence
Toxicity studies in laboratory animals are often used for hazard identification purposes, in safety studies (e.g., for chemical registration), or for insight on mode or mechanism of toxicological action. Extrapolation of animal data to humans is often challenging for chemicals in general and is more difficult with asbestos because of the complex variables that influence determination of risk, namely hazard (i.e., fiber type, size) and exposure considerations. Experimental laboratory animal studies frequently employ high exposure concentrations for the purpose of identifying hazards, although such studies may have limited direct utility for making predictions about humans, whose typical ambient exposures are much lower.

Route of exposure is another critical element when assessing the relevance of animal studies to humans. For asbestos, inhalation is a relevant route of exposure, but instillation studies involving direct placement of fibers into the lungs of laboratory animals are not relevant to humans because they bypass normal clearance mechanisms for fibers.

With these factors in mind, some general statements about animal studies and evidence can be made (EPA, 2003):

• All asbestos types are considered capable of producing pulmonary tumors and mesothelioma in experimental animal models.
• Animal studies generally show increased tumor incidence both with increasing duration of exposure and with increasing fiber concentration.
• Carcinogenic response in animal studies is likely related to fiber length, those fibers longer than 10 µm being most carcinogenic. Very short fibers (less than 2-3 µm) are not considered tumorigenic and have not produced tumors in animal studies.
• Carcinogenicity in animal models is also related to fiber diameter, with fibers finer than 0.25 µm having more carcinogenic potential than fibers whose diameter exceeds approximately 1.5 µm, the latter which have not been shown to be tumorigenic in animals.
• Chrysotile fibers appear to be less durable (i.e., biopersistent, refractory) in lung tissue than amphibole asbestos, and hence less likely to have pulmonary effects than do amphibole fibers.
• In short-term animal retention studies, chrysotile asbestos undergoes rapid, longitudinal splitting in the lung while amphiboles do not (the latter being more biopersistent).
• Multiple clearance processes operate over different time frames and some of these are strongly fiber-length dependent. Fibers shorter than approximately 10 µm appear to be cleared more rapidly than are longer fibers, while those longer than approximately 20 µm are not cleared efficiently at all.
• The role of fiber diameter in affecting clearance in animal studies is not well-delineated, although fibers that are capable of reaching the deep lung appear to be those with diameters less than 0.7 µm.

Numerous chronic inhalation toxicity studies have been conducted for various solid-state or fibrous materials ranging from amphibole asbestos to soluble glass fibers. The interpretation of these studies is often confounded by differences in fiber size distribution, ratio of long to short fibers, fiber type, and amount of non-fibrous particles present. Today, it is generally recognized that high concentrations of insoluble nuisance dusts will compromise the clearance mechanism of the lungs, causing inflammation and a tumorigenic response in the rat, events attributed to a lung overloading phenomenon. This phenomenon in the rat has been hypothesized to be associated with two threshold-related events (Oberdoester, 2002). The first threshold is the pulmonary dose that results in a reduction in macrophage mediated clearance while the second threshold, occurring at a higher dose than the first, is the dose at which antioxidant defenses are overwhelmed and pulmonary tumors develop.

The key factor that precludes direct extrapolation of these types of animal inhalation studies and effects to humans is the high level of exposure employed compared to human occupational or ambient exposures.

Because animal studies are confounded by various factors, including the “overloading effect” which has now been acknowledged to influence rat response, a recent working group convened by the International Life Sciences Institute (ILSI), in conjunction with the EPA, proposed a testing strategy for prioritizing fibers for chronic testing (ILSI, 2005). The proposed strategy included three primary components: (1) preparation and characterization of the appropriate fiber sample, (2) testing for biopersistence in vivo,
and (3) assessment of toxicologic endpoints in a subchronic rodent study. The latter of these three has been utilized in the assessment of asbestos (i.e., chrysotile) toxicity in laboratory animal experimentation.

**Recent Animal Inhalation Studies**

Bernstein et al. (2006) recently published a 90-day inhalation study in rats using a commercial chrysotile fiber to characterize the cellular and pathological response in the rat lung using the criteria developed by the International Life Sciences Institute (ILSI, 2005) and based on the European Commission (EC) guidance for the evaluation of synthetic vitreous fibers. In this study, male Wistar rats (39/group) were assigned to one of two chrysotile exposures groups, either a mean fiber aerosol concentration of 76 fibers (length >20 µm)/cm³ (3413 total fibers/cm³) or a concentration of 207 fibers (L>20 µm)/cm³ (8941 total fibers/cm³) for 6 hr/day, 5 days/wk for 13 consecutive weeks, followed by a non-exposure (recovery) period of 92 days. Control animals (having no exposure to fibers) were included in this study. Animals were evaluated at the end of exposure and at 50 and 92 days post-exposure as well. At each time point, rats were evaluated for lung fiber burden, histopathological changes, cellular proliferation response, cellular inflammation, and clinical biochemistry.

Through 90 days of exposure and 92 days of recovery, animals at the lower exposure showed no fibrosis at any time point and no difference from controls in BrdU response (indicator of cellular proliferation) or biochemical or cellular parameters. Microscopically, the long chrysotile fibers were observed to break apart into smaller particles and fibers. At the higher concentration, slight fibrosis (i.e., formation of fibrous tissue) was observed. The authors reported that at an exposure concentration 5000 times greater than the U.S. threshold limit value of 0.1 f(WHO)/cm³, chrysotile produces no significant pathological response in rats.

Bernstein et al. (2005) also extended a subchronic study (i.e., 90 days in length) on Canadian chrysotile in rats to 1 year post-exposure in order to better understand the dynamics of chrysotile clearance from the rat lung. They found that chrysotile used in the 90-day rat study had a clearance time of 11.4 days for fibers longer than 20 µm, which is similar in length to that of glass and stone wools. At 1 year after exposure, no long (L>20 µm) chrysotile fibers remained in the lung. In contrast, with amphibole asbestos, 4x10⁵ long fibers (L>20 µm) were reported to remain in the lung one year post-exposure. Based on these studies that employ current methods and techniques for evaluation of inhalation hazard, chrysotile appears to be considerably less persistent than amphibole asbestos (Bernstein et al., 2005).

**Human Evidence**

Exposure to asbestos (specific fiber types not defined) has been associated with adverse health outcomes, notably asbestosis, lung cancer, and mesothelioma (USEPA, 1986). Asbestosis, a chronic, fibrotic disease of the lung, has been documented in occupational
settings with typically higher exposures than those encountered in the ambient environment. There has been less concern about a putative link between ambient exposures and asbestosis.

Evidence that asbestosis might be linked with lung cancer began to surface in the 1930s (Lynch and Smith, 1935; Chief Inspector of Factories, 1938). Doll subsequently established what most believe to be an acceptable causal demonstration between asbestosis and lung cancer (Doll, 1955). During the 1960s, numerous studies and clinical case reports resulted in the recognition of mesothelioma as an occupational disease associated with exposure to asbestos (Bartrip, 2004). Since that time, there have been suggestions and evidence that risk factors other than asbestos (i.e., poliomyelitis vaccine) may play a role in the subsequent development of mesothelioma (Peterson et al., 1984; Wick et al., 2001; Gibbs et al., 1989), although prevailing thinking is that many cases of mesothelioma are related to exposure to certain forms of asbestos (Bartrip, 2004).

Today, there is little dispute that certain forms of asbestos are linked to asbestosis, lung cancer, and/or mesothelioma. Observation of asbestos-related disease in humans has been most easily observed in occupational settings, while demonstrating a relationship between exposure and disease is more difficult for ambient exposures. In addition, discerning the relationship between asbestos and disease involves clarifying (a) level and duration of exposure, (b) the type and size distribution of fiber, (c) the latency period between first exposure and onset of disease, (d) any confounding lifestyle factors such as smoking history, as well as co-exposures to other respiratory hazards and/or dusts, and (e) the age at which exposure occurred. Clearly, these are complex variables to be considered when assessing human health risk.

Epidemiological Studies
Hessel et al. (2005) reviewed the epidemiological evidence on asbestos and lung cancer and concluded “because of the relative insensitivity of chest radiography and the uncertain specificity of findings from histological examinations or computed tomography, that it is unlikely that epidemiology alone” can put to rest issues involving scientific fact, causal relationships, and medicolegal questions. Factors such as fiber type must be included when assessing causation. This introductory statement is relevant when evaluating epidemiological studies involving asbestos exposure and humans. Paustenbach et al. (2004) reviewed the early history of the presence of chrysotile asbestos in brake linings and pads and associated occupational hazards. Between 1930 and 1959, eight occupational exposure studies were conducted for which workers manufacturing friction products were part of the workforce assessed. The studies provided supportive evidence of asbestosis among highly exposed workers but provided little context or information on the nature of the exposures. Between 1960 and 1974, five more epidemiological studies were conducted — again looking at workers manufacturing friction products. From 1975 to 2002, more than 25 epidemiology studies were conducted to ascertain the risks of asbestos-related disease in brake mechanics, and Paustenbach et al. (2004) report
that these latter studies (i.e., 1975-2002) clearly indicate that brake mechanics were not at increased risk of adverse health effects from exposure to asbestos.

Collectively, the studies found no increased risk of asbestosis or mesothelioma in brake mechanics and no evidence that lung cancer in this occupational group could be attributed to exposure to asbestos. The authors attribute this lack of causative evidence to several factors, among them: (1) the airborne concentration of chrysotile fibers and exposure duration were too small to be significant; (2) chrysotile fibers are too short to be toxicologically important; and (3) chrysotile fibers are substantially less pathogenic than amphibole fibers in inducing lung cancer and mesothelioma. During this same time period, there were 20 additional studies that examined occupational risk among friction product manufacturing workers exposed to asbestos, exposures that were believed to be 10 to 50 times greater than those of brake mechanics (Note: asbestos forms and fiber types are not specified across the studies). Even here, there was no increased risk of asbestosis, lung cancer, or mesothelioma (Paustenbach et al., 2004).

Yarborough (2006) recently reviewed 71 asbestos cohorts and concluded that the evidence does not support the hypothesis that chrysotile, uncontaminated by amphibole fibers, causes mesothelioma. In this review, Yarborough (2006) reported that among roughly 32,853 subjects exposed to amphiboles, 404 cases of mesothelioma (1.23%) were reported, whereas only 7 cases were observed for 32,039 subject exposed to chrysotile (0.04%). Mixed fiber exposures resulted in an intermediate percentage of 0.67% for mesothelioma (994/147,384). The trend is clearly slanted towards amphiboles as a causative factor in mesothelioma induction (Gibbs et al., 1989). The available data indicate that the risk of mesothelioma in occupational settings is primarily, if not solely, due to exposure to amphibole fibers.

Wong (2001) studied auto mechanics to assess the link between malignant mesothelioma and asbestos exposure and concluded that the evidence does not support chrysotile alone as a risk factor for mesothelioma. Some of the motivation for reviewing this industry sector relates to the 1986 EPA guideline (EPA, 1986) on prevention of asbestos disease among auto mechanics, in which mesothelioma was listed as a consequence of exposure to asbestos fibers from brake linings and clutch facings. EPA had reportedly based this conclusion on case reports and not on epidemiological findings, whereas Wong relied on 6 epidemiological studies for his analysis and reported that the six reports were consistent in reporting no increased risk of malignant mesothelioma among auto mechanics. The relative risks reported in the six studies ranged from 0.62 to 1.00, and based on a meta-analysis of all studies, the relative risk was determined to be 0.90 (95% confidence interval of 0.66-1.23). Wong (2001) and Yarborough (2006) independently noted that when the weight of scientific evidence clearly points to differences with currently held regulatory views, modification of regulations should naturally follow.

In another comprehensive look at asbestos, a peer consultation effort was convened in 2003 (ERG, 2003) to discuss a proposed protocol (EPA, 2003) to assess asbestos-related
risk. After specifically evaluating the evidence related to mesothelioma, the panelists unanimously agreed that the epidemiological literature provides compelling evidence that amphibole fibers have far greater mesothelioma potency than do chrysotile fibers, an increasingly common finding and one observed in a re-analysis of 17 cohort studies (Hodgson and Darnton, 2000). Moreover, there is growing scientific consensus that chrysotile exposures do not cause mesothelioma, an observation generally consistent with the meta-analysis reported by Hodgson and Darnton (2000). These investigators conducted a comprehensive quantitative review of the relationship between asbestos fiber type and potency for causing lung cancer and mesothelioma. They concluded that amosite and crocidolite are, respectively, on the order of 100 and 500 times more potent for causing mesothelioma than is chrysotile. The evidence for this relationship relative to lung cancer was less clear, but they concluded that amphiboles were between 10 and 50 times more potent for causing lung cancer than chrysotile.

In contrast, Stayner et al. (1996) concluded that the epidemiologic evidence did not support the notion that chrysotile asbestos is less potent than amphibole for inducing lung cancer. However, based on a review of the percentage of deaths in various cohorts from mesothelioma, Stayner et al. (1996) stated that amphiboles were likely to be more potent than chrysotile in the induction of that disease. They also noted that comparisons of the potency of various forms of asbestos are severely limited by uncontrolled differences in fiber sizes. Thus, while divergent opinions still remain, there is general agreement that amphibole fibers represent a greater hazard than chrysotile.

An analysis (EPA, 2003) of epidemiological data involving different fiber types found that factors that might influence the evaluations and which should be addressed when considering causation and interpretation include:

- Limitations in air measurements when characterizing historical exposures;
- Limitations in the manner in which the character of exposure (i.e., mineralogical type, range and distribution of fiber dimensions) was measured;
- Limitations in the accuracy of mortality determinations;
- Limitations in the adequacy of the match between cohort subjects and the selected reference (control) populations.

In summary, there are complexities in the human evidence that confound the relationships between asbestos fiber type, duration and amount of exposure, and subsequent risk of disease, particularly the possible carcinogenicity or development of asbestosis at lower exposure levels than those historically present in certain occupational settings. Like the animal data, the epidemiology data generally support the following conclusions:

- Lung cancer and pleural mesothelioma have been produced by different forms of asbestos in occupational settings. The human data suggest a lower risk for chrysotile than either crocidolite or amosite.
• The risk of lung cancer is markedly higher among cigarette smokers who are also exposed to asbestos, suggesting a synergism between these risk factors. Smoking has not been identified as a significant confounder with respect to mesothelioma incidence.
• For chrysotile asbestos, the risks of lung cancer from mining operations and in the manufacture of asbestos cement and friction products have been substantially lower than in textile production. Relative to asbestos cement manufacture, the risks of lung cancer and pleural mesothelioma have been lower when chrysotile only has been used than when amphibole asbestos has been involved as a contributing exposure.
• Typically, the epidemiology studies for asbestos do not include accurate estimates or measurements of exposure, either to volume of inspired air or fiber type. Mixed exposures further confound the effort to differentiate risks posed by chrysotile and amphibole fibers.

IV. Exposure Assessment

In discussions about asbestos-related disease, one usually thinks of occupational exposures and possible risks related to commercial use and exposure. However, asbestos is ubiquitous in the environment because of its presence in the earth’s crust and dissemination of fibers from natural sources, and thus there is some, typically small, ambient exposure to humans. While this is not normally considered in asbestos risk assessments, ambient or background exposure does contribute to the body burden of all humans.

Methods of Analysis
Asbestos fibers are analyzed and quantified using either phase contrast microscopy (PCM) or electron microscopy (either scanning electron microscopy or transmission electron microscopy, SEM or TEM, respectively). Because of limitations with PCM and SEM, only TEM is capable of providing definitive information on fiber number, dimension, and morphology. PCM technology only measures fibers greater than 5 µm in length and with an aspect ratio of >3:1 (the ratio of length to width), and cannot detect fibers whose diameters are less than approximately 0.2-0.3 µm (ATSDR, 2001). A further limitation of phase contrast microscopy is that it cannot distinguish between asbestos and non-asbestos fibers or between different types of asbestos. This is an important detail when reviewing and considering historical studies with respect to risk, exposure, and disease. In nonoccupational settings, where a large fraction of the detected fibers are not asbestos (e.g., wood, cotton, glass), PCM may greatly overestimate the actual asbestos levels in air. TEM air measurements of asbestos are reported in terms of mass, fiber number, or structure number, although results expressed in different units cannot be readily compared. Thus, caution is needed when comparing data that are measured using different analytical techniques and reported in differing quantitative units.
Ambient Levels
Published data are available on asbestos concentrations in ambient, occupational, and non-occupational settings, and the following is not intended to be comprehensive, but rather is intended to provide some sense of scale or relative concentrations in these various environments. Because of differing methods used in quantitation/analysis of asbestos, recognition of differing reporting units is a necessity. Additionally, not all of the reported airborne concentrations listed below specifically delineate whether the fibers monitored were greater or less than 5 µm in length. If PCM methods were used, one can generally infer that the reported concentrations are for fibers longer than 5 µm, since this methodology cannot accurately quantify fibers shorter than 5 µm. It is important to understand the limitations of some exposure monitoring studies if fiber characteristics (i.e., length, width, type) are not included, as these have considerable bearing on the subsequent hazard potential and ultimate potential risk.

Available data concerning airborne concentrations of asbestos of the dimensions most relevant to human health (i.e., fibers longer than 5 µm) generally show average concentrations on the order of 1x 10^-5 f/ml for outdoor rural air and average concentrations up to about 10x higher in urban environments (HEI, 1991). Older estimates include ambient levels ranging from 3x10^-8 to 3x10^-6 PCM f/ml (NRC, 1984). More recent investigations report ambient levels from not-detected (ND) to 8x10^-3 PCM f/mL with a median of 3x10^-4 and mean of 5x10^-5 PCM f/mL (WHO, 1998). Finally, an analysis of monitoring data for asbestos in ambient air worldwide estimated rural and urban levels at about 1x10^-5 TEM f/mL and 1 x 10^-4 TEM f/mL, respectively (HEI, 1991). The Agency for Toxic Substances and Disease Registry (ATSDR), a division of the U.S. Department of Health and Human Services, has reported that these levels are sufficiently low that they are not likely to represent a significant health concern (ATSDR, 2001). It is important to note again the differing methods of analysis (i.e., PCM vs. TEM) just discussed.

Indoor Environments
Investigators have attempted to evaluate exposure levels of asbestos in a variety of indoor settings as well. With all exposure studies, it is important to point out that the extent to which one study is representative of conditions generally found in U.S. public and commercial buildings is not known with a high degree of certainty. Sources of variability among studies could include the types of buildings sampled, types of asbestos-containing material (ACM) present, extent of ACM damage, building selection strategy, sampling location within buildings, level of building activity, and analytical sampling methodology and analysis, among others.

The Asbestos Institute (2006) reported that following an evaluation and compilation of 1,377 air samples from 198 different ACM buildings not involved in litigation, mean indoor air levels ranged from 4 x 10^-5 to 2.4 x 10^-3 TEM f/ml (HEI 1991). Grouped by building category, the mean concentrations were virtually identical: 5.1x10^-4, 1.9x10^-4,
and $2.0 \times 10^{-4} \text{ f/ml in schools, residences and public/commercial buildings, respectively, suggesting}
that based on these measurements, background exposures, regardless of setting, are reasonably similar.

In a survey conducted by EPA (1988b), airborne concentrations of asbestos in 94 buildings that contained asbestos ranged from not detected (ND) to 0.2 TEM f/mL with an arithmetic mean concentration of $6 \times 10^{-3} \text{ TEM f/mL}$ (Spengler et al., 1989). Asbestos concentrations in 41 schools that contained asbestos ranged from ND to 0.1 TEM f/mL with an arithmetic mean of $0.03 \text{ TEM f/mL}$ (EPA, 1988b; Spengler et al., 1989).

Another study reported average concentrations of airborne asbestos fibers 5 µm in length or greater of $8.0 \times 10^{-5}$ and $2.2 \times 10^{-5} \text{ TEM f/mL}$ in 43 nonschool buildings and 73 school buildings, respectively (Chesson et al., 1990; HEI 1992, Spengler et al., 1989). The average outdoor levels of asbestos fibers found in these studies were comparable to those measured indoors (Spengler et al., 1989), again suggesting generally similar background levels and underscoring the fact that humans may be exposed to both human-derived and natural sources of asbestos.

Another study of 49 buildings in the U.S. reported mean asbestos fiber levels of $9.9 \times 10^{-5} \text{ PCM f/mL}$ in buildings with no ACM, $5.9 \times 10^{-4} \text{ PCM f/mL}$ in buildings with ACM in good condition, and $7.3 \times 10^{-4} \text{ PCM f/mL}$ in buildings with damaged ACM (WHO, 1998). The release of asbestos fibers from ACM is typically sporadic and episodic and human activity and traffic may influence the release and subsequent exposure to asbestos fibers. Direct comparison of levels inside and outside ACM buildings indicate that typical (nondisturbed) indoor levels are usually low but may be higher than outside levels (Chesson et al., 1990).

**Occupational Exposures**

Some epidemiological studies involving occupational settings include air measurements in which samples were collected only infrequently, while measurements may be lacking altogether from the earliest time periods when exposures may have been the greatest. In such cases, exposures were often estimated by extrapolation from other available measurements or by expert judgment. With few exceptions, little or no sampling was conducted prior to the 1950s when exposure concentrations were almost certainly higher than in present-day occupational settings. Most exposure measurements in these studies were based on area samples, and not on personal sampling which is a much better predictor of actual human exposure. In addition, many of the estimates of airborne asbestos concentrations from historical studies were conducted for compliance monitoring or insurance purposes and not for estimates of direct human exposure.

Occupational exposure levels vary by industry, type of work involved, sampling/analysis methods, personal protective equipment used, and engineering controls (i.e., dust-control measures) and may be up to several hundred fibers/ml in industrial settings or mines with poor dust control, but more typically are on the order of several fibers/ml or less in
modern industrial settings (Chrysotile Institute, 2006). From a broad perspective, however, occupational exposures, including work in asbestos abatement, generally fall below the OSHA (Occupational Safety and Health Administration) Permissible Exposure Limit (PEL) of $1 \times 10^{-1}$ f/mL (ATSDR, 2001), and generally appear to be well below the PEL if only fibers greater than 5 µm long are considered. Exposures to airborne asbestos in the pulp and paper industry and reported mean exposures during asbestos abatement also vary, but seem to fall in the range of $1 \times 10^{-3}$ to $2 \times 10^{-1}$ f/mL (ATSDR, 2001). Workers involved in custodial or maintenance and repair work in asbestos-containing buildings may be exposed to higher asbestos levels, although when viewed collectively across studies, 8-hr time-weighted average (TWA) exposures for personal sampling are also below the OSHA PEL of $1 \times 10^{-1}$ f/mL for fibers longer than 5 µm (ATSDR, 2001). In these reports, TEM analysis showed that over 98% of the asbestos structures were below 5 µm in length and would not have been detected or counted by PCM (Kominsky et al., 1998a, 1998b).

After 1974, most of the information on exposure of brake mechanics to airborne asbestos was gathered primarily from a series of sampling surveys conducted by the National Institute of Occupational Safety and Health (NIOSH). These surveys indicated that the TWA asbestos concentrations (approximately 1-6 hr in duration) during brake servicing were between 0.004 and 0.28 f/ml and the mean TWA was about 0.05 f/ml, a level below the current standard and the standard at the time of the sampling (Paustenbach et al., 2003). Paustenbach et al. (2003) also report that brake mechanics were not exposed to TWA concentrations above workplace exposure limits in place at the time of the study. Thus, recent occupational exposures appear to be within permissible limits, likely attributable to effective industrial hygiene practices, surveillance and monitoring, and recognition of the importance of limiting/controlling human exposures to asbestos.

**History of Occupational Exposure Levels (OELs) for Asbestos**

In recognition of asbestos as a potential occupational inhalation hazard, the U.S. Public Health Service proposed the first occupational guideline for asbestos exposure in 1938 of 5 mppcf, or 5 million particles per cubic foot. Between 1960 and 1974, five epidemiology studies of friction product manufacturing workers were conducted, and during this same time period, the first studies of brake lining wear (dust or debris) emissions were conducted, showing that automobile braking was not a substantial contributor of asbestos fibers greater than 5 µm in length (Paustenbach et al., 2004). From 1960 to 1974, the field of industrial hygiene continued to advance, and the first Federal (i.e., OSHA) TWA-PEL for asbestos was established in 1971 at a level of 12 f/cc (1 cc = 1 ml). In 1972, this level was reduced to 5 f/cc and in 1976 lowered yet again to 2 f/ml. In 1986, the OSHA PEL was lowered to 0.2 f/cc and in 1994 to 0.1 f/cc, the level where it currently stands.

**Summary**

Numerous studies have evaluated site-specific airborne asbestos concentrations, and there is some quantitative variability in the reported asbestos fiber concentrations in air
For a more detailed review of these studies, the ATSDR toxicological profile (ATSDR, 2001) for asbestos and other general reviews can be consulted (Paustenbach et al., 2004). Older buildings with ACM generally report indoor air concentrations of asbestos that are somewhat higher than outdoor air (HEI 1991; Spengler et al., 1989). However, Spengler et al. (1989) report that regardless of whether buildings do or do not contain ACM, or contain ACM that has been damaged, human exposure appears to be low, particularly when compared to permissible occupational exposure limits. Furthermore, non-occupational (i.e., ambient) exposure of the general population to asbestos in both indoor and outdoor air is generally very low.

V. Risk Characterization

Risk assessment refers to a determination of the relative risk to humans from exposure to an agent, frequently a chemical but possibly a pharmaceutical agent, a pathogen, or a natural metal such as cadmium. The cornerstones of a risk assessment are hazard identification (i.e., characterization of the toxicological profile for a substance), dose-response assessment, and exposure assessment. For asbestos, risk assessment is complicated and confounded, for both the hazard and exposure aspects of the risk equation. The EPA (2003) notes:

Although much progress has been made over the last decade toward elucidating the fiber/particle mechanisms that contribute to transport and subsequent cancer induction, at least two critical data gaps remain:

• No one has yet been able to track a specific lesion induced by asbestos in a specific cell through to the development of a specific tumor. There have been experiments that show altered DNA and other types of cellular and tissue damage that are produced in association with exposure to asbestos. Other studies have demonstrated that tumors of the type that result from asbestos exposure exhibit patterns of DNA alteration (or other kinds of cellular damage) that are sometime (but not always) consistent with the earlier cellular changes associated with asbestos exposure. There are also studies that show that exposure to asbestos can lead ultimately to development of tumors. However, these types of studies have yet to be linked;

• The specific target cells that serve as precursors to tumors in various target tissues are not known with certainty.

Thus, it appears that there is no consistent, identifiable toxicological endpoint upon which to consistently assess potential risk to humans following exposure. This is a limitation on the hazard side of the risk assessment evaluation of asbestos. Relative to challenges on the exposure side of asbestos risk assessment, historical exposure estimates are confounded by differences in fiber type, length, diameter, and lack of measures of personal exposure levels. Instead, exposure to asbestos has typically been
quantified utilizing general air concentration or even exposure reconstruction estimates, both of which are imperfect when trying to quantify risk to humans. Furthermore, while it is generally accepted that smoking is a confounder of the relationship between asbestos and lung cancer, the exact influence of smoking duration and intensity on this relationship is unknown. Despite the failure to construct consistent and validated quantitative risk estimates for humans, a qualitative risk assessment for asbestos supports the following observations:

- Among occupational groups, exposure to asbestos may pose a health hazard that could result in asbestosis, lung cancer, and/or mesothelioma. The incidence and probability of disease formation is related to fiber type, dose, confounding variables, and industrial processing.
- In non-occupational settings that involve asbestos exposure, the risks of mesothelioma and lung cancer are generally much lower than for occupationally-exposed individuals. The risk of asbestosis is very low.
- Finally, in the general population, the risks of mesothelioma and lung cancer attributable to asbestos cannot be quantified reliably and are most likely exceedingly low.

**Advances in Evaluating Asbestos Risk**

EPA's current risk assessment for asbestos is based on a review completed in 1986, and since that time, there has been substantial new information about asbestos fiber toxicity and exposure considerations. One example of the outdated nature of the EPA's assessment pertains to fiber type and length. The 1986 assessment recognizes six mineral forms of asbestos, and considers each of these with fiber sizes longer than 5 µm to be of equal carcinogenic potency, a conclusion not supported by current scientific evidence. Other assumptions in the 1986 EPA assessment, many of which are still retained today but which have little scientific support include the following:

- “Gastrointestinal cancers are also increased in most studies of occupationally exposed workers.” In fact, a recent review committee charged with evaluation of the evidence relevant to the causation of cancers of the pharynx, larynx, esophagus, stomach, colon, and rectum by asbestos concluded that only for the larynx was there sufficient evidence to support a causal relationship (nap.edu).
- “Animal studies confirm the human epidemiological results. All major asbestos varieties produce lung cancer and mesothelioma with only limited differences in carcinogenic potency.” Note, this is perhaps the single most notable difference in current thinking, as there is now substantial evidence that amphibole fibers are much more potent than chrysotile fibers.
- At the time of publication (1986), EPA estimated that the risk to the general population following a lifetime of continuous exposure to 1 x 10^-4 f/mL is 2.8 mesothelioma deaths and 0.5 excess lung cancer deaths per 100,000 females and 1.9 mesothelioma deaths and 1.7 excess lung cancer deaths per 100,000 males (EPA, 1986). While this contains information that is inconsistent with current risk estimates, the EPA did
acknowledge the limitations of its assessment. To quote, “These risks are subjective, to some extent, and also subject to the following limitations in data: 1) variability in the exposure-response relationship at high exposures; 2) uncertainty in extrapolating to exposures 1/100 as much; and 3) uncertainties in conversion of optical fiber counts to electron microscopic fiber counts or mass determinations” (EPA, 1986).

Subsequent to this assessment, the EPA published its recommended inhalation reference concentration (RfC) and carcinogenic risk assessment methodology and extrapolation for asbestos, although it did not differentiate between fiber types or relative potency (EPA, 1988). This is the standard by which asbestos risk is currently evaluated. Given the information that has been developed over the past 20 years, it has become clear to scientists, risk assessors, and even the EPA itself that changes to the approach are needed.

In light of this, EPA contracted the development of a state of the art protocol in 2001 to assess potential human health risks associated with exposure to asbestos. Subsequent to publication of this protocol, there was a peer review (ERG, 2003), during which experts versed in asbestos toxicology, epidemiology, exposure, and risk assessment convened to assess the draft EPA protocol. Because the final EPA report (EPA, 2003) encompassed many elements and recommendations from the expert peer review, the findings of the peer-review panelists will be presented first.

From the Eastern Research Group (2003) peer review summary: “The peer consultation panel strongly endorsed the conceptual approach of developing an updated cancer risk assessment methodology that takes into account fiber type and fiber dimension. The opportunity is at hand to use substantial new information from epidemiology, experimental toxicology, and exposure characterization on what continues to be an extremely important societal issue — assessing the health risks associated with environmental and occupational exposures to asbestos. The panel recommended that EPA proceed in an expeditious manner to consider the panelists’ conclusions and recommendations with a goal of having an updated asbestos risk assessment methodology. It is important that EPA devote sufficient resources so that this important task can be accomplished in a timely and scientifically sound manner. The panel urges that additional analyses underpinning the document, preparation of documentation, and further review be carried out in an open and transparent manner.”

The panelists made the following conclusions and recommendations (ERG, 2003):

*Measurement methods.* Continuing advances have been made in the application of exposure measurement technology for asbestos fibers during the past two decades. These advances include the use of transmission electron microscopy (TEM) and allied techniques (e.g., energy dispersive x-ray detection, or EDS) as an alternative to phase contrast microscopy (PCM), thereby allowing the bivariate (i.e., length and width) characterization of fibers and fiber type. The proposed risk assessment methodology incorporates these advances in the development of an exposure index.
Integration of exposure and risk assessment models. A key aspect of the proposed risk assessment methodology is a linking of specific exposure characterization methodology with exposure-response coefficients. It has been emphasized that any change in the exposure characterization metrics must be accompanied by changes in the exposure-response coefficients of the risk assessment models.

Access to additional raw data sets. The panelists strongly recommended that EPA make every attempt to acquire and analyze raw data sets from key human epidemiological studies. It would also be desirable to obtain bivariate (i.e., length and diameter) fiber exposure information for these re-analyses.

Fiber diameter. The proposed risk assessment methodology uses a diameter cut-off of 0.5 micrometers or less for considering fibers [relative to potency]. The report states that fibers 0.7 µm in diameter can reach the respiratory zone of the lung. A few panel members indicated that the fiber diameter cut-off could be as high as 1.5 µm during oral breathing. There was general agreement that the diameter cut-off should be between 0.5 and 1.5 µm.

Fiber length. Panelists agreed that there is a considerably greater risk for lung cancer for fibers longer than 10 µm. The panelists all agreed that the available data suggest that the risk for fibers less than 5 µm in length is very low and could be zero. The Berman and Crump analyses (EPA, 2003) made a significant contribution by obtaining and analyzing membrane filters from the animal inhalation studies in Edinburgh and conducting quality-assured bivariate length and distribution analyses by TEM, thereby greatly reducing the uncertainty around the exposure-response relationship for chronic fiber exposure in rats. Unfortunately, correspondingly detailed information on bivariate size distribution is not available for humans. This leads to the need to use animal data, although one must recognize the uncertainties associated with interspecies extrapolations because of differences in variables such as anatomic characteristics and respirability between species. Future analyses may benefit from using other available laboratory animal data sets and human data sets.

Fiber type. For mesothelioma, the panelists supported the use of different relative carcinogenic potencies for different fiber types. The panelists unanimously agreed that the available epidemiology studies provide compelling evidence that the carcinogenic potency of amphibole fibers is two orders of magnitude greater than that for chrysotile fibers. There was recognition that time since first exposure is an important factor in determining risk for mesothelioma and some discussion is needed on the importance of duration and intensity of exposure.

For lung cancer, the panelists had differing opinions on the inferences that can be made on the relative potency of chrysotile and amphibole fibers. Some panelists supported the finding that amphibole fibers are at least 5-fold more potent
for lung cancer than are chrysotile fibers. Other panelists did not think the statistical analyses in the draft methodology document supports this relative potency and wondered if additional review of the epidemiological data might identify factors other than fiber type.

**Cigarette smoking.** Most panelists felt strongly that future analyses need to pay more attention to the effects of smoking on the lung cancer exposure-response model and extrapolations to risk. However, the current data sets have variable and limited information available on smoking. The panelists noted that smoking is the primary cause for lung cancer, but the lung cancer dose-response relationship for smoking is complex due to the effects of smoking duration, intensity, and cessation. The impact of smoking affects both the estimation and the application of the model for projecting risk of lung cancer due to asbestos exposure. This may be an especially critical issue for low-exposure extrapolation.

Methods: The panelists also urged, in the study-specific analysis, exploration of alternative exposure-response models other than the lung cancer and mesothelioma risk models EPA has been using since 1986. This would possibly include non-linear response models (e.g., log-linear models), examination of separate effects for concentration and duration, time since first exposure, time since cessation of exposure, and different methods for measurement error. Exploration of non-linearity should also include shape of the curve in the low exposure area.

The panelists recommended alternative approaches to meta-analyses. In particular, panelists recommended meta-regression using original (untransformed) exposure-response coefficients, in which predictor variables include the estimated percentage of amphiboles, percentage of fibers greater than 10 µm, and categorical grouping of studies according to quality.

Some panelists felt that an Exposure Assessment Workshop, with participants having a broad range of expertise, could evaluate the uncertainties in historic occupational data sets’ exposure measurements. They felt such a workshop could result in a more confident assessment of exposure-response relationships for populations exposed to a variety of amphiboles, chrysotile, and mixtures. With incorporation of other available knowledge including fiber type, smoking (if available), and the relative number of excess lung cancers and mesotheliomas, it may well be possible to gain a much clearer understanding of the roles of these variables as causal factors for these asbestos-associated cancers.

**Present-Day Risk Protocol**

Following the peer review (ERG, 2003), Berman and Crump, contractors to the EPA, adopted most of the recommendations, although some of the research and analyses recommended have not yet been undertaken and/or completed. It was the opinion of Berman and Crump that “the recommended approach to risk assessment can be consid-
ered for use in the interim, while the additional research and analyses recommended by the expert panel are completed.” At that point, a final revision of this document will be developed and it is expected to serve as a component of a broader effort by the EPA to revise the Agency’s current approach for assessing asbestos-related risks.

In the final draft of the “Technical Support Document for a Protocol to Assess Asbestos-Related Risk” (EPA, 2003), Berman and Crump concluded that the existing asbestos epidemiology database consists of approximately 150 studies of which approximately 35 contain exposure data sufficient to derive quantitative exposure/response relationships. A detailed evaluation of 20 of the most recent of these studies, which includes the most recent follow-up for all of the cohorts evaluated in the 35 studies, was completed. The following conclusions result from this evaluation:

(1) To study the characteristics of asbestos that relate to risk, it is necessary to combine results (i.e., in a meta-analysis) from studies of environments having asbestos dusts of differing characteristics. More robust conclusions regarding risk can be drawn from an analysis of the set of epidemiology studies taken as a whole than results derived from individual studies.

(2) By adjusting for fiber size and fiber type, the existing database of studies can be reconciled adequately to reasonably support risk assessment.

(3) The U.S. EPA models for lung cancer and mesothelioma both appear to track the time-dependence of disease at long intervals following cessation of exposure. However, the relationship between exposure concentration and response may not be adequately described by the current models for either disease. There is some evidence that these relationships are supra-linear (i.e., convex, more than linear).

(4) Whereas the U.S. EPA model for lung cancer assumes a multiplicative relationship between smoking and asbestos, the current evidence suggests that the relationship is less than multiplicative, but possibly more complex than additive. However, even if the smoking-asbestos interaction is not multiplicative as predicted by the U.S. EPA model, exposure-response coefficients estimated from the model are still likely to relate to risk approximately proportionally and, consequently, may be used to determine an exposure index that reconciles asbestos potencies in different environments. However, adjustments to the coefficients may be required in order to use them to estimate absolute lung cancer risk for differing amounts of smoking.

(5) The optimal exposure index that best reconciles the published literature assigns equal potency to fibers longer than 10 µm and thinner than 0.4 µm and assigns no potency to fibers which do not meet these criteria.

(6) The optimal exposure index also assigns different exposure-response coefficients for chrysotile and amphibole both for lung cancer and mesothelioma. For lung cancer, the best estimate of the coefficient (potency) for chrysotile is 27% of that for amphibole, although the possibility that chrysotile and amphibole are equally potent cannot be ruled out. For mesothelioma, the best estimate of the coefficient (potency) for chrysotile is
only 0.0013 times of that for amphibole, and the possibility that pure chrysotile is non-
potent for causing mesothelioma cannot be ruled out by the epidemiology data.

(7) The exposure index and exposure-response coefficients embodied in the risk assess-
ment approach and proposed in this protocol are more consistent with the literature than
the current EPA approach. In particular, the current approach [EPA, 1986] appears high-
ly likely to seriously underestimate risk from amphiboles, while possibly overstating risk
from chrysotile. Consequently, it is recommended that the proposed approach begin to
be applied in assessment of asbestos risk on an interim basis, while further work is con-
ducted to further refine the approach.

(8) The residual inconsistency in both the lung cancer and mesothelioma potency values
is primarily driven by those calculated from Quebec chrysotile miners and from South
Carolina chrysotile textile workers. The difference in the lung cancer potency estimated
between these studies has long been the subject of scientific analysis. A detailed evalu-
ation of the studies addressing this issue, the results of our analysis of the overall epi-
demiology literature, and implications from the broader literature, indicate that the most
likely cause of the difference between these studies is the relative distribution of fiber
sizes in the two environments. It is therefore likely that the variation between these
studies can be further reduced by developing improved characterizations of the dusts that
were present in each of these environments.

VI. Summary

Although asbestos exposure, disease, and the degree to which they are associated or
causally related remains controversial, scientific evidence and analysis over the past 20
years has led to a firmer basis for understanding and predicting risk to humans. Despite
EPA’s continued reliance on an older risk model for asbestos exposure, the collective
evidence, from continued data analysis and animal study, now provides a clearer picture
of the relationship between asbestos exposure, fiber type characteristics, and the devel-
opment of lung cancer and mesothelioma. While asbestos risk assessment has historical-
ly been challenging because of difficulties with both the hazard and exposure sides of
the risk equation — and though the underlying biochemical and toxicological/pathologi-
cal mechanisms remain elusive — our ability to derive plausible predictions of risk has
improved.

To more accurately define the hazard associated with asbestos exposure, one needs to
consider differences in fiber type, length, and diameter, and how these influence differ-
ences in potency related to disease causation. While existing studies are not sufficiently
robust to support definitive identification of the toxicological mechanism(s) associated
with disease onset, through retrospective analysis of both animal and human data sets,
Berman and Crump (EPA, 2003) concluded the following, which represent statements
taken from a more extensive list of conclusions:
1. Fibers less than a minimum length of between 5 and 10 microns do not appear to contribute to risk. To the extent that fiber size is adequately characterized, the animal inhalation studies and injection/implantation studies consistently indicate lack of ability of shorter structures to contribute to the induction of cancer. Additionally, animal retention studies and histopathological evidence provide strong mechanistic evidence that explains the lack of potency for short structures, as they are readily cleared from the respiratory tract. Potency appears to increase with increasing fiber length beyond a minimum length. This observation of increased potency with increasing length appears to extend up to at least 20 µm, and potentially up to a length of 40 µm. Thus, analyses performed in support of risk assessment must provide adequate sensitivity and precision for counts of the longest structures.

2. Because fibers that contribute to the induction of cancer and respiratory disease must be respirable, they must also be thin. The majority of evidence indicates that respirable fibers are thinner than 1.5 µm and the vast majority of such structures are thinner than 0.7 µm. More specifically, there is evidence that points to a cutoff in absolute width that better defines the bounds of biological activity rather than a cutoff in the aspect ratio that has historically been used when defining fiber characteristics and the potential for risk.

3. In rodents, the magnitude of any effect of mineralogy upon cancer risk appears to be modest at best. However, for humans, mineralogy appears to be an important determinant for cancer risk with chrysotile fibers appearing less potent than amphibole fibers for inducing mesothelioma and with somewhat less certainty, lung cancer. It remains important that fiber length, width, and type are evaluated simultaneously when drawing conclusions about risk to humans. It is believed that the underlying cause(s) for the observed difference in potency between chrysotile and the amphibole fiber types may relate to differences in fiber durability, and to shape/size related differences which together influence differences in deposition, retention, or clearance.

**Current Risk Methodology**

Given the progress over the past 20 years in our understanding of the various aspects of asbestos mineralogy and its association with disease in humans, it is important that EPA revise its current risk assessment methodology to reflect this improved scientific understanding. One clear example of the need to revise the 1986 model (EPA, 1986) is illustrated by the failure of EPA to differentiate the potency of the various types of asbestos fibers, something that has now been convincingly demonstrated. The work of Berman and Crump (EPA, 2003), along with the subsequent peer review convened by ERG (2003), together provide state of the art insight and recommendations for risk assessment of asbestos which need to be considered now.

**Implications for Public Health**

Ambient asbestos exposure does not appear to be a significant risk factor for asbestosis, lung cancer, or mesothelioma for the general population. These diseases have historical-
ly been largely confined to occupational settings in which asbestos exposures were not adequately controlled, or as a result of significant overexposure, often involving years of occupational exposure. Despite some divergence from earlier thinking, more recent analyses of certain occupational settings (e.g., brake industry workers, automechanics) suggest that asbestos exposures in these industrial settings were not causally related to respiratory disease or lung cancer. Ultimately, regardless of exposure source or setting, human risk of asbestos-related disease appears to be driven by the dynamics of the exposure, namely fiber type(s) and dimensions, as well as concentration and duration of exposure. Going forward, it is hoped that the societal attention and resources allocated to asbestos will be focused on those whose exposure merits attention and control, and limited for those whose ambient exposure and subsequent risk appear negligible or certainly less than once thought.
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