



## APPLYING DEFINITIONS OF “ASBESTOS” TO ENVIRONMENTAL AND “LOW-DOSE” EXPOSURE LEVELS AND HEALTH EFFECTS, PARTICULARLY MALIGNANT MESOTHELIOMA

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**Although asbestos research has been ongoing for decades, this increased knowledge has not led to consensus in many areas of the field. Two such areas of controversy include the specific definitions of asbestos, and limitations in understanding exposure-response relationships for various asbestos types and exposure levels and disease. This document reviews the current regulatory and mineralogical definitions and how variability in these definitions has led to difficulties in the discussion and comparison of both experimental laboratory and human epidemiological studies for asbestos. This review also examines the issues of exposure measurement in both animal and human studies, and discusses the impact of these issues on determination of cause for asbestos-related diseases. Limitations include the lack of detailed characterization and limited quantification of the fibers in most studies. Associated data gaps and research needs are also enumerated in this review.**

Arguably, more is known about exposure to and disease produced by “asbestos” than for any other toxic material or group of materials. A current search of the National Library of Medicine’s database, for example, yields

10,502 references mentioning “asbestos.” This is a large underestimate of “all articles,” however; Google Scholar returns 318,000 citations that contain the word “asbestos” in the text. However, more knowledge has not led to

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more consensus about exposure-disease relationships or, in particular, about those aspects of exposure, whether physical or chemical, that are the most important disease determinants. Therefore, there is a considerable need to identify what is already known with reasonable certainty, with an emphasis on *quality studies rather than cataloguing of studies*; what may be debatable but important (data gaps); and how (and if) additional research can contribute to filling the latter. The wide variety of past, available information actually makes this task more difficult because the available information covers a long period of time and measurement methodology and animal models have varied considerably in quality over the years. *There is considerable utility in whittling the sources of information down to the most essential and informative studies rather than looking at the literature as a whole*, although it is necessary to do the latter to identify the former. Further, since "asbestos exposure" was greatest in the past, early studies (particularly of heavily exposed occupational cohorts) show a much heavier burden of disease and are likely to be more informative as to exposure-response relationships, even if they lack the sophistication of more recent studies. Recently, considerable efforts have been made to explore the past work in the context of new methodology, in terms of both exposure assessment and more accurate determination of disease. This discussion focuses on the "low end of exposure," however defined (see next section), which adds its own difficulties.

#### DEFINITIONS OF "ASBESTOS"

Asbestos is a generic term used to identify a number of well-known silicate minerals that are capable of producing thin and flexible fibers when crushed. Some of these minerals were of significant industrial and economic importance and have been used widely. The term "asbestos" has no definitive mineralogical significance but is applied to several minerals, which under certain circumstances crystallize

with an asbestiform growth habit or outward appearance of the mineral. The term "asbestiform" describes a growth habit exemplified by bundles of thin, long, separable fibers that are often flexible and are resistant to heat and chemicals. As with other minerals, different "habits" can in some cases share the same name, elemental composition, and chemical structure, as in the case of asbestiform and nonasbestiform amphiboles such as "tremolite." The mineralogical definitions in current use for "asbestos" are based on the properties that make (or made) the material valuable as a commodity, namely, long, thin, flexible fibers with high tensile strength and resistance to heat and chemicals. In the regulatory arena, six minerals were originally nominated to carry the asbestos label (U.S. Department of Labor, 1975; IARC, 1977). These include chrysotile, crocidolite (riebeckite asbestos), amosite (cummingtonite-grunerite asbestos), anthophyllite asbestos, tremolite asbestos, and actinolite asbestos. Of these, only the first three were of major significance industrially, although both anthophyllite asbestos and tremolite asbestos have been mined in the United States (UICC, 1965). In 1965, the UICC recommended that "Among the countries in which and between which studies should, if possible, be made are Australia (crocidolite), Canada (chrysotile), Cyprus (chrysotile), Finland (anthophyllite), Italy (chrysotile), South Africa (amosite, chrysotile, and crocidolite), the United States of America (chrysotile and tremolite), and the Union of Soviet Socialist Republics (chrysotile)" (UICC, 1965; Selikoff & Churg, 1965).

The inadequate and incomplete definition of "asbestos" has resulted, as noted by an IARC Consensus panel, in "taxonomic confusion and lack of standardized operating definitions for fibers." "'Asbestos' is often inappropriately used as a generic, homogeneous rubric, and even when an asbestos fiber type is specified, its source is rarely stated" (Kane et al., 1996). Mineral fibers, which are grouped under the rubric, have been divided in many ways, but

two are most common: *regulatory* definitions and *mineralogical* definitions. Regrettably, neither of these definitions corresponds to the common understanding of what “asbestos” is to most observers, and to some degree, these two approaches sometimes contradict one another.

### **Asbestos Regulatory Definitions**

Regulatory definitions specify the subset of minerals mainly used in commerce, as noted earlier, for purposes of identifying them and limiting human exposure. In addition to mineral species identification based on chemistry and crystal structure, regulatory definitions specify physical parameters, such as length and width, which apply to and define particles that meet specific counting rules. This is frequently done by identifying approved analytical methods, such as ISO 10312 (ISO, 1995) or NIOSH 7400 (NIOSH, 2003), that clearly define for the analyst which particles should and should not be counted. Historically, the most commonly used definitions (e.g., those used by the Occupational Safety and Health Administration [OSHA], National Institute for Occupational Safety and Health [NIOSH], and World Health Organization [WHO]) for a regulated form of “asbestos” are limited to those structures longer than 5  $\mu\text{m}$  and with a defined length-to-width (aspect) ratio of 3:1 or sometimes 5:1; rarer definitions (e.g., AHERA as used by the U.S. Environmental Protection Agency [EPA]) include different length parameters. Concentrations are sometimes specified in regulations; for example, some U.S. EPA regulations exculpate samples that have less than 1% asbestos mineral by weight. However, most regulations are based on numbers of countable particles per unit volume of air. Generally the regulatory definitions have evolved historically for practical reasons related to the analytical sensitivities of the instruments used in regulatory measurements. As such, they may include categories that do not produce health effects or, conversely, may exclude some that do.

Diseases are very often attributed to “asbestos” and not to the individual minerals that “asbestos” defines. This has a serious effect upon the interpretation of the mode of action of the individual asbestos minerals in the production of related diseases. There are other minerals that produce fibrous (“elongate”) dust particles, having similarity in variable physical and chemical properties to asbestos. A number of them may produce the same diseases as asbestos under certain conditions. A full discussion of these many minerals is beyond the scope of this paper, but one example is erionite (fibrous zeolite), a fibrous mineral shown to produce mesothelioma in great excess in both human epidemiological and laboratory animal studies (Baris et al., 1981; 1987; Sebastien et al., 1981; Maltoni et al., 1982; Wagner et al., 1985; Kelsey et al., 1986; Simonato et al., 1989; Metintaset al., 1999; Emri et al., 2002; Baris & Grandjean, 2006; Carbone et al., 2007). The mineral does occur naturally in North America, was reported to produce disease (Kliment et al., 2009), and is currently under investigation by the U.S. EPA in some locations (Below et al., this issue).

Another example is “balangeroite,” a mineral having been described by some as “an asbestiform fibrous silicate (exhibiting) cytotoxic and oxidative properties similar to those exerted by crocidolite asbestos” (Gazzano et al., 2005). It is associated with chrysotile in the Italian Balangero deposit (Belluso & Ferraris, 1991) and is believed by some to exert for chrysotile miners and millers there carcinogenic effects similar to those produced by tremolite associated with the Québec chrysotile deposit at the original (Bell/King/Beaver/Johnson) complex in Thetford Mines (McDonald et al., 1997; Case et al., 1997; Case & McDonald, 2008).

### **Asbestos Mineralogical Definitions**

An extensive literature exists describing the mineralogy of asbestos and asbestos-related minerals (Speil & Leineweber, 1969; Zoltai,

1981; Pooley, 1981, 1987; Veblen & Wylie, 1993; Leake, 1997, 2004; Neuendorf et al., 2005; Gunter, et al., 2007). Mineralogical definitions appear to contradict or be confused with those that are regulatory, medical or industrial (catalogued in Lowers & Meeker, 2002). While the most useful definitions would be interdisciplinary and unchanging, it has recently been suggested that “the rigor of established mineralogical terminology is critical to the research process and the ultimate understanding of the mechanisms of toxicity” (Institute of Medicine [IOM], 2009). Inevitably though, these are anything but unchanging, particularly with respect to the classification of amphibole minerals (IOM, 2009, Leake, 1997; 2004, Hawthorne & Oberti, 2007). IOM (2009) suggested in reviewing the “NIOSH Roadmap” (IOM, 2009, NIOSH, 2010) that:

Rigor in terminology may eventually be applied consistently in the regulatory setting. In creating a new acceptable paradigm for risk assessment in this area, the Roadmap should not continue the historical use of ambiguous terminology occasionally found in some existing standards and guidelines. To ensure proper scientific terms, a modern technical glossary or other standard reference text, appropriate for the field of study, should be used and cited. For example, the American Geological Institute *Glossary of Geology* may be appropriate for many of the mineralogical or geological terms (Neuendorf et al., 2005). Other reference texts should be consulted for words not found in the AGI glossary or for toxicological or epidemiological terms. Words or terms that are not scientifically or technically valid should be removed from the glossary and the text. (IOM, 2009, p. 34)

The basic chemical and crystal structural properties of the primary regulated asbestos minerals are well known to research workers involved in the study of asbestos-related disease. These minerals belong to two distinct mineralogical groups: chrysotile being a member of the serpentine mineral group; and crocidolite, amosite, tremolite asbestos, actinolite asbestos, and anthophyllite asbestos being members of the amphibole mineral group (although as noted earlier it has been recommended that actual mineralogical names, e.g.,

fibrous riebeckite rather than crocidolite, be used where possible).

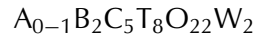
The distinction between the mineralogical groups is important when considering the aetiology of asbestos-related diseases because it demonstrates that the potential of asbestos to produce disease is not confined to one crystalline mineral or chemical grouping. The biological potential of asbestos is most likely directly related to the ability of the minerals to form fibrous dust particles, or elongated mineral particles in the parlance of the NIOSH Roadmap. This capability to produce fibrous particles is inherent in the chemical composition and physical structure of the minerals concerned and is a result of the minerals’ paragenetic history or formation regime. However, it is noteworthy that comparably sized (including length and aspect ratio) particles produced by comminution of nonfibrous analogs of the asbestos minerals have not been thoroughly tested for toxic potential and, unless and until they are, many health scientists believe that such analogs need to be treated with similar caution, as long as they meet minimum requirements for fiber length. In summary, “For regulatory and health assessment purposes . . . there is no evidence that potentially affected cells can distinguish between ‘asbestiform’ and ‘non-asbestiform’ fibers having equivalent dimensions” (Case, 1991, p. 357).

### Amphiboles<sup>1</sup>

The crystal structure of amphibole minerals, including the asbestiform varieties, is a double chain structure of linked SiO<sub>4</sub> tetrahedra, which lie parallel to the c crystallographic axis. Pairs of double chains are bound together with bridging cations to form a structural unit. The cations, which occur in the various structural sites, differ markedly among the amphibole minerals, so much so that the current mineralogical classification of the members in this mineral group is made primarily on the basis of the cation content of specific crystallographic sites (Leake et al., 1997, 2004).

<sup>1</sup>See Pooley. (1987).

A general formula for amphiboles can be written as:



where T is the tetrahedral site generally containing Si but also some amounts of Al, Ti, and Fe<sup>3+</sup>; C commonly contains Mg, Al, Ti, Fe, and Mn; B commonly contains Ca, Mg, and Na; A commonly contains Na and K; and W commonly contains OH, F, and Cl. In nature a tremendous variety of elements can be incorporated into the amphibole structure, making amphiboles an extremely diverse group with more than 80 named species.

Of the most common asbestiform amphiboles, crocidolite (fibrous riebeckite) is the asbestiform variety of the amphibole mineral riebeckite that has sodium, magnesium, and iron cations linking the SiO<sub>4</sub> tetrahedral chains. Amosite (fibrous cummingtonite-grunerite) is the asbestiform variety of the amphibole solid-solution series cummingtonite-grunerite that contains magnesium and iron cations in similar linking sites. Tremolite asbestos and actinolite asbestos are amphibole minerals that contain calcium and form a solid-solution series between the magnesium- and iron-rich end members. The iron-rich members of these calcic amphiboles are actinolite and ferro-actinolite. Anthophyllite asbestos contains mainly magnesium with varying amounts of iron in its structure. Single specimens of each of the amphibole minerals are often considered to be part of a larger solid-solution series (Hawthorne & Oberti, 2007). The cations located in the various structural sites of the amphibole minerals help define their crystal structures and their unit cell parameters. All of the amphiboles that have been observed to grow in the fibrous habit have a monoclinic crystal symmetry with the exception of anthophyllite, which is orthorhombic.

The elongate particles produced by the asbestiform amphibole minerals are considered to be generated by the splitting of weakly bound crystallites or fibrils away from an aggregate or bundle (Franco et al., 1970;

Hutchinson et al., 1975). The particular morphology of amphibole asbestos particles is, therefore, mainly the result of the nucleation and preferential growth of crystallites in the fiber axis or *c* crystallographic direction. This is a feature that is often referred to in the description of hand specimens of asbestos ore as cross-veined or slip-veined fiber. Asbestiform fibers can also form by in situ alteration of other minerals in the natural environment (Meeker et al., 2003). It should be noted, however, that although all amphibole minerals have a similar chainlike crystal structure, *they do not all break down to form fibrous particles with the same physical dimensions as those of the fibrous and asbestiform amphiboles. Asbestiform amphiboles are geographically rare in comparison to their nonasbestiform analogues.*

In general, for many reasons, amphibole minerals most frequently do not grow in fibrous or asbestiform habits. In addition, the same amphibole minerals that do occur and are classified as "asbestos" can also be found as samples that are not fibrous or asbestiform in habit. Short (<5 μm length) tremolite particles, for example, were identified by transmission electron microscopy (almost always usually in the absence of detection of longer, thinner, asbestiform tremolite fibers) in the majority of lungs of American schoolchildren examined (Case et al., 1994).

Larger single amphibole crystals can also break readily along certain planes parallel to the *c* crystallographic axis, resulting in the formation of a good prismatic cleavage that readily produces elongated particles that are not fibrous or asbestiform. These particles have often been referred to in the asbestos community as cleavage fragments. Note that these particles are produced by breaking, not by growth as are the fibrous and asbestiform amphibole particles. Some regulations (OSHA, 1992) specifically exclude cleavage fragments from asbestos counting rules even though many cleavage fragments actually meet the counting rule requirements. OSHA (1992) also acknowledges that it is commonly not possible to distinguish single cleavage fragments from asbestiform fibers during analysis and

provides guidance to the analyst that “when in doubt count.” Since the 1992 OSHA rulemaking regarding cleavage fragments, considerable debate has occurred in the asbestos community regarding the potential toxicity of long, thin cleavage fragments. NIOSH (NIOSH, 2010; IOM, 2009) still considers amphibole cleavage fragments that meet counting requirements potentially toxic and advises that they not be excluded during analysis.

### Serpentines

The only serpentine mineral classified as asbestos is chrysotile. However, it is not the only mineral in the serpentine group that can occur in a fibrous form. Mineralogical studies of chrysotile samples (Whittaker, 1956a, 1956b, 1956c; Yada, 1967) showed it to be a sheet silicate, the sheet structure of which is curled into a cylindrical scroll-like form apparently around a central capillary. The sheet structure of chrysotile is similar to that of the clay mineral kaolinite, with magnesium rather than aluminum in its structure. The structure is composed of a layer of linked  $\text{SiO}_4$  tetrahedra with all three oxygens at the base of each tetrahedra being shared. The second half of the sheet, the “brucite” layer, is attached at the apex of the tetrahedral. This layer contains magnesium, oxygen, and hydroxyl ions octahedrally coordinated, with oxygen being shared between the brucite and silica layers. Due to a mismatch in the dimensions of the brucite and silica layers, an extensive two-dimensional sheetlike structure can only be obtained by curvature of the sheet with the brucite layer outermost. This is the reason for the scroll-like structure of chrysotile and the production of concentric cylindrical tubes that we know as chrysotile fibrils. When chrysotile fibrils are formed, a particular radius of curvature may be the most stable so that the diameter of fibrils, whatever their source geographically, is approximately the same, being of the order of 30 nm. The mismatch in the structure of serpentine mineral can be accommodated in other ways, which have resulted in the formation of the other serpentine minerals, lizardite, and antigorite.

Chemically, chrysotile is a simple magnesium silicate with a ratio of three magnesium cations to two silicon atoms. However, iron, nickel, and manganese can replace magnesium in the brucite layer, and aluminum can also replace silicon in small amounts. Traces of chromium, cobalt, scandium, and the alkali earth metals are also often incorporated in the brucite layer in place of magnesium (Morgan & Holmes, 1971). The other serpentine minerals lizardite and antigorite cannot be chemically distinguished from chrysotile. These other serpentine minerals normally occur as massive fine-grained specimens but can be found in a fibrous form that yields particles that more closely resemble particles of the amphibole asbestos minerals. The serpentine minerals lizardite and antigorite are far more common geologically than chrysotile, which occurs in serpentine rocks either in cross-veined or slip fiber formations. The chrysotile fiber from cross-veined formations is more highly prized for its fiber length and purity.

### Characteristics of Asbestos Dust Particles

There exists a great diversity in the size and morphology of dust particles produced from the various asbestos-related minerals. The most significant differences are those between the dust particles liberated from the serpentine asbestos chrysotile and the amphibole varieties of fibrous and asbestiform minerals. In general, the fibrous amphiboles have fibers, which are often rigid and parallel-sided. These fibers have a quadrilateral or polygonal cross section, with variable size distributions of width to length ratios that are dependent upon the mineral type and its geological source. Amphibole asbestos mineral from sources of a commercial grade produce dust containing fibers that are longer and finer than fibers from any other sources. A characteristic feature of the dust produced by amphibole asbestos minerals from different geological sources is that they will consist of fibers with a distinct size distribution of fiber diameters. This distinction in fiber size characteristics does not apply to variations in

fiber length distributions of commercial-grade asbestos, which are more closely related to the mechanical treatment that the mineral sample may have received in the production of the dust. Fibrous amphibole samples can, therefore, be found with identical chemistry and atomic structure but with a diversity of crystalline form or growth habit. This variation in crystal habit of a given species is almost certainly due to variations in the conditions under which it crystallized. The morphology of chrysotile asbestos dust particles is distinctive when compared with the amphibole mineral varieties. They generally consist of uniformly sized fibrils that occur either singly or as bundles and aggregates. The proportions of each of these components in a chrysotile dust vary considerably, depending upon the manner in which the dust was generated and also upon the geologic source and grade of the sample. The size and appearance of single chrysotile fibrils are unique to this mineral and can help in its identification. Chrysotile asbestos bundles are not physically stable, and their instability can often be demonstrated by their ability to readily disperse in water into single chrysotile fibrils.

### Discussion of Implications of Definitions

Mineralogical definitions, such as those just discussed, unlike regulatory or industrial specifications, are based on a scientific rather than an operational classification, but they have varied considerably over time. The most authoritative source on nomenclature is the International Mineralogical Association (IMA), although the nomenclature is in the form of "recommendations." The variation over time makes usage of such definitions problematic for amphibole minerals; for example, amphibole nomenclature has been revised by the IMA Committee on Amphibole Nomenclature three times since 1978. This leads to real problems for regulators and for health scientists attempting to use accurate definitions, as these may (like some disease classifications) prove to be a "moving target." Further, as noted by the Institute of Medicine and National Research

Council's recent review of the NIOSH roadmap for research on asbestos fibers:

These changes in mineral names far outpace the ability of the rulemaking and legislative processes in the United States and have caused considerable confusion and misunderstanding, as is evident in recent legal actions relating to asbestos contamination in Libby, Montana. [In addition], the correct application of IMA amphibole nomenclature . . . requires analytical precision and accuracy that is generally beyond the capability of the standard asbestos analysis methods used for exposure assessment purposes. This presents difficulties for the comparison of analytical results between, and even within, laboratories. (IOM, 2009, p. 37)

The critical need for application of accurate scientific terminology in research on asbestos-related minerals, coupled with the realities facing analysts, regulators, and lawmakers, presents a conundrum for the asbestos community.

Recent attempts at better and more comprehensive and comprehensible terminology regarding fibers has been developed in the "NIOSH Roadmap" (NIOSH, 2010). The Institute of Medicine (IOM) review of the NIOSH Roadmap (IOM, 2009) makes additional suggestions in this regard. For health science, what is really needed is an operational definition of "structures that can cause disease," an apparently simple task that has proved elusive nonetheless. Of particular importance to biological researchers and health scientists, there is a need to understand that there are differences between "cleavage fragments," "fibers," and "acicular crystals" (among other terms), even if those particles cannot always be distinguished during an analysis. The NIOSH Roadmap approach (NIOSH, 2010, IOM, 2009) aims to use the term "elongated mineral particle" to describe all of these particles if specific attributes are applicable to a broad class of particle types.

The potential for individual particles of asbestos dust to cause disease has always been closely linked with their size, as defined by the length and diameter of individual fibers. For more than three decades, it has been considered by scientific panels for government agencies (Timbrell et al., 1971; ATSDR, 2003)

that fibers shorter than 5  $\mu\text{m}$  in length have insignificant carcinogenic potential and that the risk to health increases with exposure to longer fibers, particularly for lung cancer. For lung cancer, fibers longer than 20  $\mu\text{m}$  and thinner than 0.3  $\mu\text{m}$  are of particular concern as demonstrated in animal studies (Berman et al., 1995), human epidemiology (Berman and Crump, 2008a; 2008b), and, most recently, models combining dimensional parameters of actual archived industrial hygiene filters in human occupationally exposed populations at high lung cancer risk (Dement et al., 2008a, 2008b; Loomis et al., 2009). Longer, thinner fibers were also found to be most hazardous in mesothelioma both in laboratory animal (Stanton et al., 1977, 1981; Miller et al., 1999) and human studies (Berman & Crump, 2008a, 2008b). Nevertheless, some observers still do not absolve the shorter structures (between 0.5 and 5.0  $\mu\text{m}$ ), in part based on their greater number in dust clouds and in lung retention (Dodson et al., 2003, reviewed in Aust et al., this issue).

The situation has recently been seen to be quite complex for asbestosis because contrary to what might be expected for chrysotile miners and millers, length of lung-retained tremolite fibers is inversely proportional to the degree (or grade) of fibrosis (Churg et al., 1989, 1993; Churg & Vedal, 1994; Nayebzadeh et al., 2001, 2006). Interpretation of the data in these studies, however, is very complex because, among other difficulties (Case, 1994):

- The dimensional distributions of fibers retained in lung may not fully reflect those initially inhaled.
- Other properties of fibers, such as aerodynamic diameter fiber equivalent, affect inhalation.
- Intrapulmonary mechanisms impacting deposition and clearance modify parameters of recovered fiber, including dimensions.
- Changes to fibers including dimensional changes and distribution while in the lung may be important in disease production.
- Disease may alter dimensions of retained fibers.

- Fiber counting protocols can introduce possible errors.

As an example, with respect to the inverse relationship between tremolite fiber length and fibrosis grade in some studies (mentioned earlier), if the fiber distribution is lognormal but the absolute concentration of fibers goes up to very high levels as fibrosis severity increases, the practical limitations of fiber analysis make the shorter tremolite fibers the ones most likely to be found. Unless these variables are taken into account (which requires characterization of the fiber length, diameter, and thickness distributions in more detail than often available), it is difficult to reach absolute conclusions.

The growth habit of the asbestiform minerals provides the basis for the formation of a fibrous dust, but the size characteristics of the individual fibers contained are controlled by the manner in which the minerals form over geological time. The fiber size characteristics will in part define whether these particles will be inhalable or respirable. Fiber size will, together with chemical factors, dictate the degree and rapidity with which fibers are cleared from the lung or retained. There appears to be sparse information in the literature to indicate the respirable size range of fibers in asbestos dust clouds. The biological potential of asbestos fibers can be defined to a great extent by the combined measurement of their lengths and diameters (bivariate size distribution), and any approach to the assessment of risk to health from exposure to fibers must be based upon their detailed characterization.

#### **MEASUREMENT OF “ASBESTOS” EXPOSURE: STRATEGIES USED HISTORICALLY AND CURRENTLY AND THEIR RELEVANCE TO ENVIRONMENTAL, INCIDENTAL, AND “LOW-DOSE” SITUATIONS**

##### **Animal Exposures**

Accurate and meaningful exposure measurement has been the bane of much asbestos science. This is due to the complexity of



the exercise. In general, there is a difference between human exposure and "animal exposure" (whether *in vivo* or *in vitro*) that makes the latter difficult to extrapolate to humans. Dosage and potentially effects are not truly comparable: For the majority of animal studies reported in the literature, exposure has been done at high concentrations expressed in mass concentrations (typically  $\text{mg}/\text{m}^3$ ). Few studies in animals reported exposure concentrations based on fiber number, and none are directly applicable to the lowest human doses of concern except by extrapolation. Routes of asbestos delivery for animal studies *in vivo* have been by inhalation, instillation, and injection. *In vitro* studies can give results that are irrelevant to human situations. *In vitro* lysis of red cells by magnesium associated with chrysotile fiber, for example, mentioned in many papers (Harrington et al., 1971; Brody & Hill, 1983), is now only of historical interest, as it is not relevant to actual human exposures. Although animal studies of the past have produced specific histopathological endpoints, such as bronchoalveolar metaplasia, diffuse interstitial fibrosis, and fiber localization within lung tissue compartments, these concentrations exceed human exposure conditions and lack specific delineation of critical exposure characteristics, such as fiber number and fiber size. Each of these disparities creates a number of difficulties in extrapolation to human exposure conditions.

Differences in sensitivity or susceptibility of various animal models to fiber exposure may also confound or mislead the extrapolation of animal findings to humans. Direct injection studies (e.g., intraperitoneal or intrapleural), although useful in studies of mechanisms, do not realistically reproduce human exposure delivery and are difficult to calibrate to actual human internal dose. Inhalation studies in laboratory animals can also be insensitive for some disease outcomes, particularly mesothelioma, perhaps due in part to differences in life span between animals and humans and in the period of latency required to produce mesothelioma.

The closer animal exposure models are to those of humans (in terms of species, lung structure, use of inhalation as opposed to injection

models, exposure, and delivered dose of similar structures), the more relevant they are to human toxicology. Results from animal studies that are dissimilar in any of these (and many other) respects should be looked upon with caution unless quantitative adjustments of key parameters, such as with the use of dosimetry models, can be employed (Asgharian & Yu, 1988; Yu et al., 1991; Yu & Asgharian, 1993; Asgharian & Anjivel, 1998). Pinkerton and associates (1983, 1986, 1989) found that airway branching patterns in the rodent lung strongly influence asbestos fiber location in terms of number and size that can be correlated to the extent of lung injury observed.

In contrast, some animal studies have been instrumental in elucidating early events of following asbestos exposures to demonstrate the importance of site-specific response to inhaled fibers. This type of work has clarified with sites of deposition, demonstrating initial sites of injury, and consequent inflammation with epithelial cell damage, inflammatory cell recruitment, and release of mediators. The latter include those stimulating either repair or progressive epithelial-mesenchymal changes leading to scarring and fibrosis (Brody et al., 1981a, 1981b, 1984a, 1984b, 1985, 1986, 1989; Pinkerton et al., 1983, 1984, 1986; Warheit et al., 1984).

Animal inhalation studies have been less effective in aiding the understanding of the impact of low-level exposure to fibers. Historically, most exposures involve extremely high-dose exposures over a prolonged period of time (Wagner, et al., 1974, Davis et al., 1978; Pinkerton et al., 1986). Short-term fiber exposure studies that might mimic incidental exposure to asbestos fibers typically fail to go beyond 1 mo postexposure time frames (Brody et al., 1981a, 1981b, 1984a, 1984b, 1985) to demonstrate the consequences of long-term recovery from such events beyond 1 mo. However, short-term exposure to asbestos fibers in animals has proven to be effective in demonstrating the potential for other environmental pollutants to enhance the retention of fibers in the lungs (Pinkerton et al., 1989). New studies to determine such chronic effects

are needed, coupled with a better understanding at the cellular and molecular level of the eventual effects and fate of fibers retained at initial sites of deposition and/or transported to other sites within the lungs or to more distant potential target sites. Examples are specific areas within pleural and subpleural tissues, peritoneal tissues, ovarian serosa, etc. The latter are perhaps best addressed in long-term animal studies, given the many difficulties encountered in human studies of retained fibers, which are subject to tissue cross-contamination and at best reflect a static representation of fiber content at the end of a long process.

### Human Exposures

In characterization of human exposures, studies vary in the degree of detail of their apparent fiber characterization and quantification, but in fact all studies are imperfect.

**Studies Based on Recall and Classification of Exposure** One of the most common approaches in human studies is to ask those who may have been exposed—with or without disease—what jobs or other circumstances existed in which they may have been exposed and then to base apparent exposure information on their responses. This asking may be direct or indirect.

Direct queries usually operate by means of questionnaire. These may simply relate to occupational histories, but ideally they should also include occupational histories of spouse, siblings, and parents, as well as residential history. The latter is useful in establishing neighborhood exposures, such as those that may have been encountered near asbestos product or processing plants, shipyards, mines, known deposits, etc. An example is a questionnaire sent to possible former residents of the small and remote crocidolite-mining town of Wittenoom, Australia:

Between 1991 and 1993 a questionnaire was sent to all former residents of Wittenoom traced to an address in Australia, (N = 3,244, 64%), excepting those participating in a cancer prevention program (N = 641, 13%) from whom the information had already been collected. Date, length and place of residence at Wittenoom, occupation at

Wittenoom, whether lived with an asbestos worker or washed the clothes of an asbestos worker, smoking and past medical history as well as demographic information were collected. (Hansen et al., 1998b; Reid et al., 2008, p. 2338)

For studies limited to occupational exposures, other sources of information may exist that allow identification of occupational groupings that may have included exposed individuals. These can be coded as to likelihood of exposure in categories (McDonald & McDonald, 1980), semiquantitatively in relation to job or occupational titles or industry groups (simple classifications or job-exposure matrices (JEM), or most “semiquantitatively” by having experienced industrial hygienists and/ or chemists code likelihood, frequency, and intensity of exposures (Siemiatycki, 1991; Pintos et al., 2009). None of these strategies are truly amenable to direct translation to actual exposure measurements other than duration. There have been some attempts to do so (Iwatsubo et al., 1998). Iwatsubo et al. (1998) generally used more modest descriptors, such as “possible” and “definite” exposure. However, hygienists’ evaluations attempted to “translate” their categorical assessments of frequency, probability, and intensity of exposure into estimated “fibers/ml-years” (cumulative exposures), realizing the tentative nature of such estimates by actually *placing them in quotation marks in the paper*:

Because no measurements of airborne asbestos levels were available, all estimations of exposure parameters were based on the experts’ subjectivity [sic], that is, semiquantification [sic], to which we subsequently assigned weight factors. This index of cumulative exposure was expressed in terms of fibers/ml-years inside quotation (“f/ml-years”). (Iwatsubo et al., 1998, p. 135)

Even for categories of exposure, the authors noted that “The experts themselves . . . reported sometimes encountering difficulties in distinguishing between sporadic and irregular exposure and between low and moderate exposure. Moreover, they suggested that the quality of their assessment for the periods under consideration (20 or more years ago) might not be as good as for more recent years

because of the lack of published data for these periods" (Iwatsubo et al., 1998, p. 138).

A problem with such estimates (whether used as categories or with more questionable "semiquantitative measures" having actual values attached as just described) is that they lack gold-standard comparisons with actual measurement (usually because none exists), and even, in most cases, any cross-disciplinary measurement of reliability. In a few instances, cross-disciplinary measurement of reliability has been obtained; for example, lung-retained fiber content significantly reflected job-based estimates in some studies, albeit at a low level (Takahashi et al., 1994). Nevertheless, the statement of the Ontario Royal Commission remains generally true for epidemiology: One of the weakest parts of all asbestos epidemiology is the quality of the quantitative exposure data (Dupré et al., 1984).

While questionnaire approaches have been most used in case-control studies of mesothelioma for both cases and controls (Siemiatycki, 1991; Teschke et al., 1997; Case et al., 2002; Peto et al., 2009; Pintos et al., 2009; Rake et al., 2009), they have also been used for lung cancer (Pintos et al., 2008) and other possible disease endpoints. Questionnaires may be administered by mail, by telephone, or through in-person interviews to either cases themselves (and controls) and, in the case of deceased individuals, next of kin. Limiting study to still-living cases (Peto et al., 2009; Rake et al., 2009) may reduce numbers but improve accuracy of recall.

#### **Studies Based on Direct Measurement**

Studies in which estimates of individual exposure are based on actual measurements, usually of area air samples but in the "best case" from personal samplers, are usually limited to cohort studies. This is natural because these tend to be studies of heavily exposed individuals in which air monitoring may have taken place on a regular or intermittent basis. Measurement technology has improved over the years. Many past studies used instruments that measured particles rather than fibers (Gibbs, 1970; Gibbs & Lachance, 1972). When such studies are referred to in relation to others

or compared to others which used, for example, the membrane filter method for optical fiber (PCM NIOSH 7400) counting, conversion factors must be used, and these may vary from one workplace or exposure situation to another. This does not mean information from past studies can be discarded, as it may be the most useful available; cohort follow-ups (McDonald et al., 1980; Liddell et al., 1997) may necessitate using the same types of measure, even if better measures have become available. There has been much dispute about "which measure to use" in such situations, but as Gilson noted at the New York Conference (Selikoff and Churg, 1965) in 1964:

Everybody is unwilling to start using a particular method of counting or a particular instrument because they say we do not know whether it is the one that is the best. You never know unless you start using one consistently for a period of time, and observing the people whose environment you are measuring with a particular instrument . . . Surely, the way to start is to choose a method at some time . . . If a decision had been made to make systematic measurements 30 years ago, with almost any instrument, you would by now, in fact, have got quite a long way to getting a dose-response relationship in this industry. (Gilson, 1965, p. 335)

There are, in fact, few situations or epidemiological studies in which direct individual exposure measurements have been obtained for use in any quantity (and with varying quality). At best, there are ambient (static, general area) measurements that are sporadic and few in number. When these are used, their use is often criticized; the large and useful body of knowledge on people heavily exposed to Wittenoom crocidolite (both occupationally and environmentally), for example, was critiqued by those who did the actual measurements due to what they believed was a small underlying number of "fiber" measurements. Rogers and Major (2002) wrote:

The only attempt at fibre level monitoring was made in the Colonial Gorge mine and mill by one of us (G.M.) in 1966 over 12 shifts, when the then modern mill was operating at full capacity. During this time, some 38 'static' samples were collected using two Casella Long Running Thermal Precipitators. In addition, three 'clean air' samples were taken (about) 100 m outside the mill which,

when recounted in 1986, indicated levels between 0.5 and 2.0 fibres/ml. (p. 127)

The authors “singled out” here responded:

In 1983 we endeavoured to make the best use that we could of the available dust measurements in order, at least, to look at internal dose–response relationships, in addition to documenting disease incidences and mortality ratios for the workforce as a whole. In 1991 we carried out similar work on a cohort of residents of the township of Wittenoom who were known not to have worked for the Australian Blue Asbestos Company . . . We also engaged the assistance of the mine and mill supervisors, the company management and government mines inspectors to assist in interpolating and extrapolating between jobs, and, with the help of the much-criticized results of the earlier konimeter surveys, to estimate historical exposures. This exercise permitted us to attribute fibre/ml exposures to the various job categories.

A validation of our estimates was published that shows clear agreement with lung fibre burden (de Klerk et al., 1996) and, based on the ‘guesstimates’, data also showed clear dose–response relationships between exposure and all asbestos-related diseases in this cohort. (Musk and De Klerk, 2002, p.128–129) (Reference to “koniometer surveys” refers to the particle-based measurements referred to by Rogers and Major (2002) above, taken with “koniometers” or “midget impingers” and requiring conversion factors for fiber estimation. Rogers and Major (2002) noted that in fact, “Many hundreds of such measurements were recorded for the early 1950s until 1966.” As in the Quebec chrysotile studies, where thousands of such measurements (from midget impinger per Gibbs and Lachance, 1972) were available, the data did indeed exist but relied on conversions which were difficult to perform).

Most recently, at least in two cohorts of asbestos textile workers principally exposed to chrysotile (Dement et al., 2008a, 2008b; Stayner et al., 2008; Loomis et al., 2009) the existence of some archived membrane filters proved useful in determinations of past exposures and their nature, at least with respect to fiber dimensions in relation to lung cancer. Loomis et al. (2009), for example, used 77 of 333 historical membrane filter samples in North Carolina plants, archived from the period 1964–1971. These were examined by electron microscopy for fiber dimension and then applied to a wider database of exposure information (including pre-1964 estimates

converted from midget impinger [particle] samples) and applied to lung cancer outcomes (of 181 cases with any mention of lung cancer on death certificate). Results were consistent with those predicted by laboratory animal studies: strongest associations with lung cancer for cumulative exposure to fibers 20–40  $\mu\text{m}$  in length. Overall, when compared to three biologically based models for lung cancer, “Best fit was obtained with an index based on Lippmann’s suggestion that fibers  $>10 \mu\text{m}$  long and 0.3–1.0  $\mu\text{m}$  thick should be most relevant to lung cancer risk (Lippmann, 1988). [However,] the change in risk per [interquartile range] was modestly greater . . . for the index proposed by Berman et al. (1995) which assigns empirical weights for relative potency to fibers in the categories  $<0.3 \mu\text{m}$  in diameter and 5–40  $\mu\text{m}$  long,  $<0.3 \mu\text{m}$  in diameter and  $>40 \mu\text{m}$  long and  $>3 \mu\text{m}$  in diameter and  $>40 \mu\text{m}$  long” (Loomis et al., 2010, p. 582). A range closer to the “Stanton model” originally derived from pleural implantation study (fibers longer than 10  $\mu\text{m}$  and thinner than 0.25  $\mu\text{m}$ ) was also significantly associated with lung cancer outcome but not as strongly.

In general, then, the exposure information on which all of our approaches (including risk assessments) are based is consistent with what we expect from toxicological understanding with respect to fiber dimensions, but it is sparse. Information on fiber type, which is relevant to biopersistence, is better, but pure single-fiber-type human exposures throughout a lifetime history are still more the exception than the rule, even for synthetic fibers (McDonald et al., 1990; Marsh et al., 2001; Pintos et al., 2009). As noted by the World Health Organization, “There are distinct differences in the propensity of the different asbestos fiber types to cause mesothelioma. Amphibole (amosite and crocidolite) asbestos is considerably more potent than chrysotile, and crocidolite is more dangerous than amosite. *The exact ratio among these three fibers depends upon the approach used to investigate the problem*” (Travis et al., 2004, p. 129; emphasis added). The latter makes preferable *general* statements like the preceding one, as well as that by a panel convened

in 2003 by the U.S. Environmental Protection Agency (EPA) (Eastern Research Group, I, 2003) which “unanimously agreed (for mesothelioma) 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” (p. viii). Such statements may be preferable to exact ratios, which generally are stated without confidence limits or even uncertainty levels.

### **Direct Measurement Techniques: Choice of Instrument and Resolution**

Assessment of exposure (and subsequent deposited or retained inhaled fiber burdens) also depends upon the choice of instrument, measurement protocol, and, once the instrument and protocol are chosen, other parameters, such as magnification used. Phase-contrast microscopy (PCM) has been the default protocol for most measurements historically, using specified models, such as NIOSH 7400 (NIOSH, 2003). Most frequently, such methods, variants of which are also used by OSHA and WHO, specify fiber length of longer than 5  $\mu\text{m}$  and width *greater than* 0.25  $\mu\text{m}$  (and sometimes *less than* 3  $\mu\text{m}$ ) having aspect ratio (length: width) equal to or greater than 3:1 (sometimes 5:1). The choice of diameter was made on the basis of the resolution of the instrument at the magnification used. Transmission (or, if at adequate resolution, scanning) electron microscopy (TEM, SEM) can be used at much higher magnifications and therefore resolve much thinner fibers, and, as important, can in association with other techniques (such as energy-dispersive spectrometry of x-rays [EDS or EDXA]) identify elemental composition of fibers and therefore “fiber type.”

Methods of sample preparation, counting protocols, and other technical parameters are also important. Although new methods are being developed to apply to the problem (Harper et al., 2008), TEM alone does not generally allow the distinction between structures that may or may not fall into some categories

of mineralogical definition as discussed in the first section of this paper. As noted by Sebastien (1991), “To be able to tell whether fibers are asbestiform or not under the [electron] microscope is quite impossible. To me, the concept of ‘asbestiform’ is not a microscopic one. Geologists may tell us whether a fiber is asbestiform, but certainly, the microscopist cannot” (p. 505).

If all else is equal, it is evident that a method such as TEM at high magnification will count more fibers at lower diameters than will a light-microscopy-based method when directly compared. Care must be taken not to compare analyses from the two methods directly in terms of risk assessment. For example, in the North Carolina TEM study using 77 archived membrane filters from asbestos textile mills, “Total cumulative exposure to fibers among the 3803 workers included in the cohort was far greater when estimated by TEM (mean 989.4 f-y/ml lagged 10 years) compared to the estimate obtained by PCM methods (mean 59.2 f-y/ml lagged 10 years).” This did not of course “change risk,” and indeed, “The strength of the association with lung cancer was similar for all TEM and PCM exposure indicators” (Loomis et al., 2010, p. 582).

### **Tissue “Burden” Studies**

Techniques for the recovery of fibers or the characteristic coated fibers known as “asbestos bodies” have been used for many decades, as early as 1932 (Stewart et al., 1932) but mainly beginning in the mid-20th century (Davis, 1964; Cauna et al., 1965; Anjilvel & Thurlbeck, 1966; Meurman, 1966). There are many studies (see also Aust et al., this issue) that report lung-retained fibers (“lung burden”), recovered from bronchoalveolar lavage (BAL) (De Vuyst et al., 1982; Sebastien et al., 1988; Dodson et al., 1991), and even asbestos bodies (and in Turkey “zeolite bodies”) or fibers recovered from sputum (Smith & Naylor, 1972; Roggli et al., 1980; Sebastien et al., 1981, 1984; Musk et al., 1983; Dodson et al., 1989). Asbestos bodies recovered from sputum were found in more than 75% of subjects in a study of 173

vermiculite workers (8 female) in Libby, MT, and increased with subject age and exposure. Asbestos body concentrations in sputum predicted radiological changes as well or better than exposures estimated from work histories and air measurements. A 2006 workshop convened by ATSDR and reported by the Eastern Research Group (ATSDR, 2006) examined the relative merits of fiber recovery methods in detail.

Extensive work in fiber or asbestos body recovery from lung tissue has been performed by many of the authors of this journal issue (Abraham, Case, Dodson, and Pooley), with too many references to mention. More rarely, recovery has included other tissues, including omentum and mesentery (Dodson et al., 2000, 2001), lymph nodal tissue (Dodson et al., 2000), and, of particular interest, pleural tissues (Boutin et al., 1996; Dodson & Atkinson, 2006). For nonpulmonary tissues, care must be taken to avoid cross-contamination with lung tissue when using autopsy or surgical pathology specimens that also contain lung (Case, 1994). Sampling of the actual parietal pleura (as opposed to mesothelioma tumor tissue or pleural plaques) is also technically difficult, and negative results are likely in individual cases due to the sparse and heterogeneous distribution of fibers when present (Case, 1994; De Vuyst et al., 1998). Unfortunately, it is difficult to compare cases from one laboratory to another due to methodological differences; control values should be provided not only from laboratory "blanks," but also from population controls where possible, matched as closely as possible. This is important because in the past normal populations have had measurable asbestos lung content that was found to increase with age and rural-urban status (Case & Sebastien, 1987; Case et al., 1988, 1994; McDonald et al., 1989; Dodson et al., 1999).

Most of the caveats applicable to assessment of fibers in the environment are applicable to these studies (other than those of asbestos bodies), as well as additional concerns, including technical aspects of tissue removal (chemical digestion versus low-temperature ashing) and the intrapulmonary mechanics

applicable to fibers, including but not limited to clearance. Interlaboratory specimen analysis is another method to assess comparisons between results from different authors, but such studies are few. Gylseth et al. (1985), for example, found in an international comparison that "Within each laboratory the ranking of the results was similar, but there were marked differences in the absolute values obtained by the different laboratories" (p. 107). They concluded, and it is now generally accepted, that for tissue burden studies, laboratories may produce "internally consistent results" but it is difficult and probably inappropriate to directly compare results from one laboratory to another. However, different laboratories that analyzed the same samples may demonstrate comparability (Case & Abraham, 2009). In reading the literature on such results, care should be taken as well to note detection limits, how they are determined, what effects might be for levels below the limits, and how they are interpreted (Abraham, 2006). Laboratories that do this type of work should, therefore, have good control values.

#### **"ENVIRONMENTAL" EXPOSURE TO ASBESTOS OR "LOW-DOSE" EXPOSURE TO ASBESTOS?: SCOPE OF THIS DISCUSSION**

The preceding sections have discussed current issues related to both defining what is and is not "asbestos," and how to identify, classify, and quantify asbestos. This section focuses on the nature of exposures that are the principal concern of this document. This section does not discuss "occupational" exposures, although it is impossible (and unwise) not to use what has been learned from the study of well-characterized occupational exposures (see earlier discussion) in relation to equally well-defined disease outcomes, particularly where extrapolation to other scenarios is possible and often necessary. Also, this section discusses mainly exposures that occur in, or as a result of, the *external* environment. This also excludes asbestos exposures in the

so-called built (or indoor) environment, sometimes referred to as “asbestos in place” or “asbestos in buildings.” The exclusion is not because this type of exposure lacks importance but because it has already been much studied; in particular, the work done under the auspices of the Health Effects Institute (HEI) is important in this regard (Health Effects Institute, Asbestos Research, 1991). It is important to remember, however, that whether discussing amosite in the historical deposits of South Africa or erionite in the tufts of Cappadocia, exposures are to minerals that first occurred in the natural, undisturbed external environment but that ultimately occurred in their most lethal forms “indoors,” at many levels of concentration, from the engine rooms of ships to the factory floor to the simple whitewash of the houses of Karain. In this sense, *all* exposures are “environmental,” or began as such. Furthermore, since mesothelioma incidence peaked around the turn of the century and has now “plateaued” and (according to most recent SEER data: Price and Ware, 1997, 2004, 2009; Moolgavkar, 2009) is slowly declining in the United States, it is likely that the *proportion* (but not necessarily, as some have incorrectly stated, the absolute number) of cases due to environmental exposures is likely to increase in coming years.

#### **“Naturally Occurring Asbestos” (NOA)**

As asbestos minerals occur in nature, there are situations of potential exposure that result from proximity of human habitation or activity to mineral deposits. Some such exposures have been referred to as “naturally occurring asbestos” (NOA), usually defined as asbestos mineral occurrences that have not been exploited commercially, (Dyken & Wheeler, 2008; Harper, 2008; Lee et al., 2008) or as asbestos found in its natural geologic setting or transported from that setting by natural processes. The minerals from these occurrences may be clearly “asbestiform” in the most stringent definition but are often either nonasbestiform or clearly fibrous while lacking formal mineralogical morphologic features

of asbestiform minerals. This has led to disagreements over the degree to which such exposures may be a health concern (Lee et al., 2008). This is an overly simplistic argument, since all forms of the mineral can and do occur in nature; it is the *capacity for exposure* (sometimes referred to as “pathways”) coupled with the ability of individual mineral samples to cause disease—something that is often unknown a priori—that most concerns the research and public health community. The term “NOA” itself is in fact unfortunate because ultimately all asbestos is “naturally” occurring (that is, derived from a natural source). Exposure that may occur through weathering and transport processes is made more likely by past manipulation or exploitation. Persons living within 40 km of chrysotile mines have been shown to have increased levels of lung chrysotile under conditions of continuing mining activity (Case & Sebastien, 1987), although without evidence of asbestos-related disease. Conversely, a small increase in the amphibole content of rocks (mixed asbestiform and nonasbestiform) near Thetford Mines, Quebec, also showed increased tremolite lung content. This rise in lung-retained tremolite was directly related to time lived in the area, inversely related to distance from mines, and associated with increased mesothelioma incidence among female residents (Case, 1991; Case et al., 2002). However, this did not appear to be due to “environmental” exposure, in that all but one mesothelioma case had some combination of occupational and/or domestic (household) exposure.

Even without mineral exploitation, Pan and colleagues (2005) showed an ecological association between “the distance [from latitude and longitude of address at initial diagnosis from California Cancer Registry records] to the edge of the nearest known body of ultramafic rock.” Although this is not actually distance to nearest asbestos deposit, a possible source of significant error, reasoning was based on the observation that while “No maps exist that illustrate the distribution of NOA in California . . . ultramafic rocks are the principal source of asbestos and may be used as a proxy for its

natural occurrence" (Pan et al., 2005, p. 1020). While this study has been criticized based principally on its ecological design (Brodkin et al., 2006), probably its weakest points are use of residence at time of diagnosis (when causation occurred decades earlier) and the assumption (unavoidable if the study were to be done at all) that ultramafic rock location is a marker of "asbestos exposure." Nevertheless, the positive result argues that, in fact, the location *is* such a marker; what is now needed is breakdown of the results to more specific and individual exposures and disease, especially in areas such as El Dorado County, California, where there is good reason to believe that exposure and disease risk exist in specific locations (but not in others). This has been shown in studies describing localized variations in mineral chemistry and morphology in the community of El Dorado Hills (Meeker et al., 2006) and identification at a particular road intersection in the county of "asbestiform . . . amphibole fibers . . . completely within the tremolite and actinolite fields, as defined by Leake and others" (Lowers & Meeker, 2007). An analysis of dog lungs, including those of two dogs who were resident at the same road intersection, showed clear excess of tremolite asbestos by transmission and scanning electron microscopy (Case & Abraham, 2009). This is, in fact, one example among many of identification of potential human exposures through use of lung-retained fiber analysis from animal sentinel populations, including goats (Dumortier et al., 2002) and cows (Fornero et al., 2009). As noted by Fornero et al. (2009), "Sentinel animals are an excellent model to assess breathable environmental background because it is possible to eliminate some variables, such as unknown occupational exposure."

It is important to understand that *an environmental exposure is not always a low-level exposure*. The degree of exposure will depend on other factors, particularly the degree to which the existing environmental source is disturbed by anthropogenic (e.g., construction, road building) or natural (e.g., weathering, landslide) events. This applies also to the extent of exposure over time (cumulative exposure). For some diseases, the mineral type (especially

for mesothelioma; Berman & Crump, 2008a, 2008b) and/or fiber length (especially for lung cancer; Berman & Crump, 2008a, 2008b; Dement et al., 2009; Loomis et al., 2009) of asbestos fibers present will also play an important role. It is therefore vital that asbestos deposits that may provide human exposures be well characterized mineralogically using techniques that allow identification of fiber chemistry and dimensions. There is also a need to have a clear understanding of the exposure "pathways" and the extent to which these are likely to result in exposure under a variety of conditions over time for these deposits.

**"Legacy Exposures" to Asbestos From Previous Commercial Sites, Including but Not Limited to Mining, Milling, Shipyards, and Distribution of Asbestos-Containing Materials (ACM) for Unconventional Uses in Neighborhoods**

There are no longer any asbestos mines functioning in the United States; the last (King City Asbestos Mine, California) closed in 2002. U.S. asbestos imports for consumption decreased from 2530 metric tons to 1460 metric tons from 2005 to 2008 (89% from Canada) (Virta, 2010). Although more than 30 states had mines, planned mines, or identified occurrences at one time (Van Gosen, 2005, 2006, 2007, 2008), the last producing and exporting mine (King City Asbestos Corporation of California) closed in 2002, marking "the end of more than 120 years of continuous asbestos production in the United States" (U.S. Geological Survey, 2003). Production peaked at 136,000 metric tons in 1973 (Kelly & Matos, 2010). Also in 2002, "In Canada, Jeffrey Mine Inc. shut down its mining operation in response to declining prices and markets" (U.S. Geological Survey, 2003). However, recent reports indicate that this mine may reopen underground (*Canadian Mining Journal*, 2010). The principal vermiculite mine in the United States, located in Libby, MT, which was identified at the time of discovery as an asbestos mine, contained large quantities of mixed amphibole (historically referred to as "tremolite" and as "sodium-rich tremolite" but



including tremolite, richterite, and winchite). Work here resulted in exposures with a high mesothelioma-proportional mortality as well as excess lung cancer and other pulmonary disease in miners and millers (McDonald et al., 2004; Sullivan, 2007). Since the mine closed in 1990, emphasis has been on disease in the community. It is sometimes difficult to sort out past occupational or domestic exposures from “true environmental” exposures in this community. However, peer-reviewed journal papers document an excess of both malignant mesothelioma (Whitehouse et al., 2008) and nonmalignant pleural disease (Peipins et al., 2003) in residents. An implied excess of asbestosis in residents based on ATSDR figures was false; all asbestosis cases reported in the literature have, with the exception of one case (the spouse of a miner), been among miners and millers (Price, 2007), although a case was also reported of an extraction plant worker who had only brief exposure many decades earlier (Wright et al., 2002). Currently, there are ongoing studies examining the health effects in the Libby community. A recent report noted increased cough, shortness of breath, and bloody phlegm production in the last year in those who had been under age 18 years when the mine closed 10 years before the questionnaire (Vinikoor et al., 2010). Mesothelioma, lung cancer, and non-malignant lung disease deaths among workers are of the same order as those observed in crocidolite miners in Australia and South Africa (McDonald et al., 2004). Other vermiculite mines having lower concentrations of amphibole mineral have not shown disease excess (McDonald et al., 1988; Hessel & Sluis-Cremer, 1989). Conversely, U.S. vermiculite transformation plants have shown pleural disease patterns similar to those observed among Libby residents (Horton et al., 2008; Rohs et al., 2008).

There are few identified U.S. plants still making asbestos products, although the most recent general figures indicate asbestos (mostly short-fiber chrysotile; 83% from Canada) “consumption” was 1460 metric tons for 2008, mostly (65 to 70%) for roofing products but also for “diaphragms used by the chlor-alkali industry, gaskets, and unknown applications” (Virta,

2009). Many other imported products are listed as “asbestos-containing,” but in most instances these are both small in number and questionable as to whether there is really “asbestos” content (Table 6, “Imports of products with basis of asbestos in 2008,” in Virta, 2009). Old ships under repair or destruction (“ship-breaking”) could constitute a current source of exposure in U.S. shipyards, but we are unaware of details of such activities. Generally, most current potential occupational asbestos exposure situations are thought to involve asbestos already installed in products, especially for buildings with asbestos-containing materials (ACM) that are undergoing asbestos abatement, extensive renovation, or demolition, and particularly in the construction industry (INSPQ, 2005; Dufresne et al., 2009).

The lack of current operational mining, industrial, or shipyard exposures does not mean that there are no current exposures as a result of such sources in the past. We call these “legacy exposures” to distinguish them from exposure due to current industrial sources, but they originated in industry and have resulted in disease incidence in many countries, including the United States. They occur from material in waste dumps, material left in sites where the fibers were used or transported, and in applications where materials were made from the fibers, including certain forms of asbestos “scrap.” The latter include road and yard surfacings. An example of the scope of the ongoing potential problem is seen in the fact that in the U.S. Environmental Protection Agency Toxics Release Inventory, 57 industrial facilities (mostly waste-management companies) reported releasing or disposing of about 20.5 million pounds (9300 metric tons) of friable (readily crumbled) asbestos in 2001 (Toxics Chemical Release Inventory, 2003).

Legacy exposures remind us of past neighborhood environmental exposures that occurred when the industries that produced them were still extant and that often resulted in community disease, particularly mesothelioma. While it is important to recognize that in many instances the exposures so generated no longer exist (although diseases attributable to them may still occur), they are instructive nonetheless

and are described here. This is not a comprehensive list, nor is it meant to be; it is important to identify *the most important studies* or often *groups of studies*—something that has not been done in other sections for this workshop. “Counting studies” is not a proper approach, as studies vary considerably in quality. Furthermore, unless scientists have spent many years reading this literature, they will not have a feel for separating the wheat from the chaff.

Prioritization of studies is exceptionally important, and some rudimentary lines of reasoning and questioning may be followed:

1. Are epidemiological studies based on *analytical* epidemiology—that is, are they cohort or case-control studies as opposed to case reports or collections of cases?
  2. For analytical epidemiology studies that are cohort-based, are the size and definitions of the cohorts adequate to be informative (many are not); are there follow-ups; and to what degree do those follow-ups inform on missing data in the original studies, environmentally exposed groups if the initial studies were of occupational cohorts, etc.? Three good examples are:
    - a. The extensive studies of Quebec chrysotile miners and millers and of residents of that region (McDonald et al., 1971, 1974, 1980, 1989, 1993, 1997, 1999; McDonald & Liddell, 1979; Churg et al., 1984, 1989, 1993; Liddell et al., 1984, 1997; Churg, 1986; 1988; Churg & Wiggs, 1986; Sebastien et al., 1986; Case & Sebastien, 1987; Churg & DePaoli, 1988; Churg & Wright, 1989; Becklake & Case, 1994; McDonald & McDonald, 1995, 1997; Case et al., 1997, 2002; Case & Dufresne, 1997; Camus et al., 1998, 2002).
    - b. Australian (Wittenoom) miners and millers of crocidolite and residents of that region (Milne, 1976; Hobbs et al., 1980; Armstrong et al., 1984, 1988; Cookson et al., 1986; de Klerk et al., 1989, 1996; Berry, 1991; Rogers, 1992; Hansen et al., 1993, 1998a; Rogers & Nevill, 1995; Alfonso et al., 2004; Berry et al., 2004; Reid et al., 2005, 2007, 2008a, 2008b, 2009; Musk et al., 2008).
    - c. Studies conducted around the asbestos cement plant using crocidolite in Casale Monferrato, Italy (Magnani et al., 1993, 1995, 1997, 2000, 2001; Magnani & Leporati, 1998; Magnani, 2001; Ferrante et al., 2007; Maule et al., 2007; Dreassi et al., 2008).
- In each of these situations, environmental and/or domestic (household) exposures led to asbestos-related disease, most seriously mesothelioma, and always (even when chrysotile was also used or primarily mined) in the presence of asbestiform amphiboles. The current epidemic of mesothelioma in Jefferson Parish, Louisiana, was predictable on the basis of the presence of asbestos manufacturing plants and shipyards in the area. (Enterline & Henderson, 1987)
3. How well-defined—and using what methodology—are exposures and dose defined in the studies or groups of studies? In general, exposures are defined using varied strategies as outlined earlier in human epidemiological studies, but most are estimates and few are sufficiently detailed to be very informative as to identify those parameters of exposure to fibers that have etiological significance. Studies that estimate dose (that is, inhaled fibers deposited or retained) are even fewer in number and more difficult to identify. Even many toxicological studies are deficient in the latter and, in the most basic ways, fail to identify the most elemental characteristics of fibers in many instances, including fiber type, dimensions, growth habits, and, perhaps most important, biopersistence as mediated by clearance. Again, it is paramount to use the best studies, but what constitutes “the best” may be a subject of debate.
  4. In human (epidemiological) studies, how well-defined are *outcomes*? Although these would seem to be simple enough in terms of disease entities (e.g., sites of cancer occurrence, asbestosis, etc.), they ultimately are reliant on one of two types of data:

death certificates or incidence figures. Both are flawed in many ways. For example, deaths from mesothelioma may be underestimated by death certificates (Lilienfeld & Gunderson, 1986; Okello et al., 2009), although this is highly variable from country to country, as in comparing Brazil (Pinheiro et al., 2003) with France (Iwatsubo et al., 2002), and within countries. Conversely, incidence figures (new cases of mesothelioma) may overestimate cases due to pathologic misdiagnosis or miscoding (Goldberg et al., 2006; Case et al., 2008). The best “cure” for the latter is rigorous pathologic confirmation of each and every case, but this is often not possible across a whole population. For example, U.S. SEER data have been limited to about 17% of the population, although corrections have most recently been applied and numbers of participating cancer registries have increased (Spirtas et al., 1986, 1994; Connelly et al., 1987; Enterline & Henderson, 1987; Price, 1997; Pinheiro et al., 2004; Price & Ware, 2004, 2009; Weill et al., 2004; Larson et al., 2007; Teta et al., 2008; Moolgavkar et al., 2009).

5. One category of epidemiological study requires special comment when one is concerned with environmental exposures: ecological studies. Because they simply identify excesses of disease in specific circumstances (most frequently geographical areas), these studies are subject to spurious associations since individual exposures are never known—an excess of a type of disease or pathology in a particular area can have many explanations not related to an overall average excess of an exposure or other circumstance in that area. This is the ecological fallacy. Nevertheless, a great deal of useful information that ultimately led to the establishment of causal associations through more robust study began with ecological studies of mesothelioma. The classical examples are the studies of Wagner and colleagues (1960) and of Newhouse and Thompson (1965a, 1965b). With specific respect to Wagner, his notes provided

to Case by Dr. Margaret Wagner in 2004 (Case, 2008) described how the process played out:

At first, the link to crocidolite seemed tenuous; the first patients were “housewives, shepherds, farmers, lawyers, and insurance agents” (Wagner, 1965). A visiting American pathologist, Steiner, had seen such cases and not only agreed with the diagnosis but told Wagner that his team “. . . had the largest collection of this very rare tumour in the world.” But as of 1957, they were unsure of the cause, positing theories of complications of tuberculosis, viral infection “on its own” (Ebstein-Barr virus had been associated with Burkitt’s lymphoma by this time), or radioactivity (thorium ore was present geologically in the same area). Wagner however clearly preferred as explanatory the “association with blue asbestos,” mostly on geographical considerations. The first 16 cases all were from the same region and (only) four worked in the asbestos industry. Some had Asbestos Bodies (AB) in the lungs. Wagner realized the importance of establishing the relationship:

“Two thoughts occurred in me: firstly that minor exposure to asbestos dust could lead to the development of a previously unrecognised but fatal tumour, and secondly that they might occur many years after the initial exposure.” He realized the implications, if he were correct, not only to industry workers but also for “risks to those living in the vicinity of the asbestos mines and mills.” (Case, 2008, p. 14)

Ecological studies retain power to detect *potential* problems, especially through the detection of lesions, such as mesothelioma, which are largely due to exposure in specific areas. More examples are given later, but at the simplest level, looking at a county-by-county (or, if the geographical areas involved are small, country-by-country) analysis of mesothelioma age-adjusted death rates can show us potential areas of concern, although we must remember that current death rates (and incidence) represent exposures in the distant past, which often no longer exist. Examples include current very high rates in the taconite-mining counties (Koochiching, Carlton, and St.-Louis) of Minnesota; in Lincoln County, Montana; in Jefferson Parish, Louisiana; in Somerset County, New Jersey (home of the original Johns-Manville plants); and—currently the highest level in the nation—in shipbuilding counties,

**TABLE 1.** Malignant mesothelioma highest age-adjusted death rates by county, from NIOSH 2008. NIOSH Table reproduced with permission from NIOSH Table 7–10 (NIOSH, 2008).

Ref. No. 2007T07-10

*Malignant Mesothelioma: Mortality*

**Table 7-10. Malignant mesothelioma: Counties with highest age-adjusted death rates (per million population), U.S. residents age 15 and over, 2000–2004**

County	State	Age-Adjusted Rate	Crude Rate	Number of Deaths	% Female
Sagadahoc County	Maine	97.1	102.6	15	26.7
Koochiching County	Minnesota	77.5	104.5	6	0.0
Lincoln County	Montana	56.1	65.1	5	40.0
Mason County	West Virginia	55.6	65.7	7	14.3
Carlton County	Minnesota	55.3	60.5	8	0.0
Lincoln County	Maine	55.0	76.0	11	9.1
Bonner County	Idaho	50.7	58.2	9	11.1
Washington County	Maine	50.3	64.7	9	11.1
Newport News City	Virginia	49.2	42.4	29	6.9
Kitsap County	Washington	48.0	43.1	40	20.0
Posey County	Indiana	47.8	46.9	5	60.0
York County	Virginia	47.2	38.8	9	11.1
Dickinson County	Michigan	47.0	63.1	7	28.6
Tooele County	Utah	46.9	36.3	6	16.7
Union County	Oregon	45.5	50.4	5	40.0
Tyler County	Texas	44.7	59.3	5	0.0
Jasper County	Indiana	43.3	41.5	5	40.0
Isle of Wight County	Virginia	42.8	40.1	5	20.0
Jefferson Parish	Louisiana	42.1	41.7	75	34.7
Somerset County	New Jersey	41.0	37.2	45	33.3
Portsmouth City	Virginia	40.5	43.6	17	29.4
Mason County	Washington	39.6	47.7	10	0.0
Martin County	Minnesota	38.6	57.5	5	0.0
Orange County	Texas	38.4	39.2	13	7.7
Hancock County	West Virginia	38.0	52.4	7	14.3
Houghton County	Michigan	37.7	40.3	6	50.0
Gloucester County	Virginia	37.5	35.0	5	0.0
Franklin County	Washington	37.4	26.2	5	20.0
Alpena County	Michigan	36.4	47.1	6	16.7
Delaware County	Oklahoma	35.7	45.8	7	28.6
Anchorage Borough	Alaska	35.6	13.7	14	0.0
Yuba County	California	34.8	30.2	7	28.6
Polk County	Wisconsin	34.8	40.7	7	0.0
Gloucester County	New Jersey	34.8	32.7	34	11.8
Kenosha County	Wisconsin	34.4	31.5	19	26.3
Niagara County	New York	34.3	40.9	36	16.7
Mason County	Michigan	34.2	42.8	5	20.0
Augusta County	Virginia	34.1	33.0	9	11.1
James City County	Virginia	33.8	42.6	9	22.2
Preble County	Ohio	33.6	35.3	6	50.0
Greenup County	Kentucky	33.4	39.5	6	33.3
Natrona County	Wyoming	32.9	33.5	9	0.0
Jackson County	Mississippi	32.5	27.0	14	21.4
Chesapeake City	Virginia	32.3	23.9	19	5.3
Clinton County	Illinois	32.2	34.7	5	40.0
Windham County	Connecticut	31.9	31.6	14	35.7
Hill County	Texas	31.7	37.4	5	20.0
Cattaraugus County	New York	31.5	35.9	12	25.0
Siskiyou County	California	31.3	44.2	8	12.5
St. Louis County	Minnesota	31.3	38.4	32	6.3
<b>Overall United States</b>		<b>11.5</b>	<b>11.3</b>	<b>12,895</b>	<b>18.9</b>

NOTE: Only counties with at least 5 deaths from the disease of interest are included. See selected limitations for general cautions regarding inferences based on small numbers of deaths, and see appendices for source description, methods, and ICD codes.

SOURCE: National Center for Health Statistics multiple cause-of-death data. Population estimates from U.S. Census Bureau.

such as Sagadahoc County, Maine (NIOSH, 2008) (see also Table 1, taken from NIOSH, 2008). Because a high male ratio is most likely to indicate an occupational origin, areas with

greater female proportions are of particular concern for possible environmental (or domestic) exposures. On the other hand, observation of Table 1 shows that actual numbers of

cases vary considerably, and one or two cases might affect rates disproportionately; longer term trends may be of greatest importance, and simple observations like this must always be backed up by true epidemiological study. Indeed, had Lincoln County, Montana, had one less mesothelioma death in the period outlined, it would not have met the criteria for inclusion at all (at least five cases), rather than appearing with the third highest county death rate. Other counties stand out because of high case numbers coupled with high rates, such as the counties in Minnesota near the taconite mines (combined, the three already named here contribute 46 cases to Table 1, all at rates above 31 per million per year (age-adjusted; ages 15 years or over, for the most recent 5 years). However, fully 44 of the 46 are male, a strong indication that an occupational exposure may be responsible. On the other hand, in Jefferson Parish, Louisiana, where there were asbestos plants and shipyards and use of ACM (including crocidolite) to cover driveways, schoolyards, and even day care centers (Case & Abraham, 2009), there were 75 deaths at a rate of 42.1 deaths per million population, of which 34.7% were female.

The high rates in some counties again take us back to the importance of mineralogical definitions and the debates they engender in the face of such epidemiological data. Areas in which there is a clear excess of diseases, such as mesothelioma, are often juxtaposed with mineralogical characterizations that seem clearly to some extent to fall into categories of elongate mineral fibers without classically asbestiform growth habit or morphology. The following areas fall within this category:

- a. Certain Minnesota counties, which currently have among the highest mesothelioma rates in the United States and in which taconite is mined (see later discussion).
- b. Past excesses near talc mining areas in upstate New York (Hull et al., 2002).
- c. Where disease is not prominent but future risk arguably is, such as some parts of El Dorado County, California (Case & Abraham, 2009).

Some health scientists understandably remain skeptical about any suggestion that mineralogical characterizations suggesting lack of fibrous or asbestiform habit suggest lack of risk in the presence of demonstrated risk, but on the other hand other explanations are possible, such as alternative exposure sources (“commercial asbestos in jobs held both inside and outside of the mining industry”) present in areas of mesothelioma excess for which “taconite” itself could not adequately explain risk (Brunner et al., 2008, Wilson et al., 2008). The debate is a crucial one, since regulatory focus and resources targeted for prevention must be concentrated on those areas of exposure that represent the greatest preventable risk.

#### **OTHER NONOCCUPATIONAL EXPOSURES**

*Household or domestic exposures* (sometimes misnamed “bystander” exposures, a term that corresponds better to para-occupational exposures) are not by definition “environmental” but can certainly be informative for analogous “true” environmental exposures. They are also likely to persist as a cause of mesothelioma for at least as long as past occupational exposures, and probably longer, since victims may be exposed as children (Rake et al. [2009] found a relationship between living with an exposed worker under age 30 years and mesothelioma incidence). Household exposure can be identified through retained lung fiber data, which may be intermediate between environmental and occupational content, as was demonstrated for women in the Québec chrysotile mining region for tremolite (Case, 1991). However, the range of individual levels may vary, and care must be taken to distinguish such exposures from environmental or occupational exposures in the same regions; this may only be possible through detailed history.

True environmental exposures—that is, exposures from either natural or legacy industrial sources—can also be a result of misclassification of occupational or household exposure. One example was provided by a misinterpretation of exposures to women in the

Québec mining regions. Camus and colleagues enlisted an international panel of experts to estimate occupational, household and environmental (“neighborhood”) exposure in the area; lifetime cumulative exposure was estimated (with considerable uncertainty) at an average of 16 fibers/cc-year. The authors found “no measurable excess risk of death due to lung cancer among women in two chrysotile-asbestos-mining regions”; the U.S. EPA (1986) model overestimated the risk of asbestos-induced lung cancer by “at least a factor of 10.” However, seven deaths from pleural cancer (ICD9 163.0) were identified during the same time frame (Camus et al., 1998), all in the higher tremolite Thetford Mines area. An accompanying commentary (Landrigan, 1998) assumed these were due to “environmental” exposure, but ascertainment of individual data by questionnaire determined that of 10 cases in the area among women, all but 1 had occupational and/or household exposures (Case et al., 2002).

Nevertheless, there is no doubt that, despite the difficulty of isolating them from occupational and household sources, environmental exposures do result in mesothelioma cases in some instances. For tremolite asbestos, for example, outbreaks have been identified in Turkey, Greece, Corsica, New Caledonia, and Cyprus (Constantopoulos, 2008). For crocidolite, environmental outbreaks have been identified in parts of China (Liu et al., 1990; Luo et al., 2003); near mines in South Africa (White et al., 2007) and in Australia (Reid et al., 2007, 2009); and in the neighborhood of asbestos plants using the fiber, usually but not always in combination with chrysotile to make asbestos cement pipe, in the United Kingdom (Newhouse et al., 1965a, 1965b), Italy (Magnani et al., 2001a, 2001b; Maule et al., 2007), Japan (Kurumatani & Kumagai, 2008), and the United States (Case & Abraham, 2009).

Two points must be emphasized again: first, that it is difficult to separate household (and often occupational) exposures from “environmental” or “neighborhood” exposures in such studies, and second, that all of the studies

have been performed in areas of high levels of exposure. This problem was addressed by Bourdes et al. (2000) in a meta-analysis that includes many of the exposure situations mentioned already. The authors concluded that for a small subset of eight studies that “provided results on pleural or peritoneal mesothelioma from household or neighborhood exposure by inhalation” and had “clearly defined exposed and unexposed groups, including those using an ecological approach”:

The combined RR for neighborhood exposure was 7.0 (95% CI:  $1.8 \pm 7.0$ ). There was a non-significant increased risk in the two studies considering mainly chrysotile exposure . . . The combined RR of pleural mesothelioma from household exposure was 8.1 (95% CI:  $5.3 \pm 12$ ). All but one study were conducted in areas at either predominant or concomitant amphibole exposure, a fact that limited the analysis according to fiber type. (Bourdes et al., 2000, p. 413)

The authors cautioned that while the selected studies showed relatively clear risk increases, the studies included in the meta-analysis addressed circumstances of exposure to relatively high levels of asbestos. No epidemiological studies are available on more common situations such as exposure in buildings, in schools, or in the general urban environment. The results of our meta-analysis are therefore likely to overestimate the risk of environmental asbestos exposure experienced by residents of industrialized countries without a specific source of exposure; they are, however, useful to indicate a *plausible upper range of the risk from environmental asbestos exposure* (emphasis added) (Bourdes et al., 2000, p. 415).

#### **ROLE OF EXTRAPOLATION FROM HIGH DOSE IN THE ESTIMATION OF ENVIRONMENTAL RISK**

While clear excesses of both household and neighborhood exposures and resultant mesothelioma incidence have been identified in areas of high past industrial exposure (see earlier discussion), it is more difficult to project

environmental risk where it has not yet been identified but must be assessed for purposes of risk assessment and public health protection (for example, at Superfund sites). In this situation it is customary to estimate risks using existing approaches, extrapolating from epidemiological studies (and sometimes animal studies) where exposure has occurred at high levels, usually in an occupational setting. When the mode of action is not known (and as is seen in the rest of this and accompanying documents it generally *is not known* for asbestos-related diseases, particularly mesothelioma, which is most important at low dose), it is conventional to apply the linear no-threshold approach. A recent state-of-the-science workshop on this subject (White et al., 2009) noted that:

Most, but not all, workshop participants concluded that for population-level risk analyses, in the absence of MOA-based dose-response models, the most appropriate low-dose extrapolation approach for both cancer and noncancer end points is linear, no-threshold extrapolation from the range of observed responses, recognizing the effects of population variability as well as additivity to background disease and exposures on the dose-response function. (White et al., 2009, p. 285)

However, this is notably as indicated *in the absence of MOA-based dose-response models*. Due to increased understanding of biological processes of disease induction, MOA-based approaches have been used more frequently both quantitatively and qualitatively (U.S. EPA, 2005). It is important in this context to understand that “mode of action” does not necessarily require a full understanding of all disease mechanisms to be useful in risk assessment or to extrapolation to risk at lower doses (White et al., 2009).

For example, without knowing mechanisms, McDonald et al. (2004) concluded on the basis of their assessment of mortality in vermiculite miners and millers at Libby, MT, that:

Probably the most robust measure of occupational risk is provided by the all cause linear model which estimates a 14% increase in mortality after 100 f/ml

years exposure that is, 0.14% increase per fibre/ml year. This estimate was obtained from workers exposed for about eight hours a day, 240 days a year. If we assume that relative risk from residential exposure is also proportional to cumulative exposure, which is potentially for 24 hours a day for 365 days per year, the appropriate increment is  $0.14 \times (24/8) \times (365/240)$  or 0.64% per f/ml years. Thus over a lifetime of, say, 50 years, an ambient exposure level of 0.1 f/ml would imply under this model an excess risk of 3.2% in all cause mortality (RR = 1.032) a not insignificant impact. Exposures of this magnitude may indeed be relevant to the residents of Libby, Montana and perhaps even in some construction areas in northern California. (McDonald et al., 2004, p. 365)

Nevertheless, the degree of uncertainty in MOA-based approaches is often great, and the default assumption often reverts to a standard linear no-threshold inference approach, especially for cancer outcomes (asbestos-related mesothelioma at low dose included). In addition, so many approaches are available, each with its own uncertainties, and exposure assessment itself is so fraught with uncertainties, that risk assessors increasingly turn to a *range of possibilities* using a range of exposure-response or dose-response models, which leads to a range of possible projected incomes in areas of potential concern. An example is a very recent draft public health consultation offered for public comment by the Agency for Toxic Substances and Disease Registry (ATSDR) in the NOA situation of El Dorado County, California. A risk estimate based on an exposure-response model for lifetime estimated risk of mesothelioma and lung cancer combined varied from a low end of 0.1 per 10,000 to a high end of 22 per 10,000—or two to three orders of magnitude (ATSDR, 2010). Even with this, the agency cautioned that “ranges do not indicate confidence intervals, merely the range of risks predicted for each model for various activity level, gender, and exposure concentration assumptions.”

In summary, extrapolation from high to low risk, whether based on inferential statistical (e.g., linear no-threshold) models or mode-of-action-based models, is fraught with uncertainty.

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