

Heterogeneity of exposure and attribution of mesothelioma: Trends and strategies in two American counties.

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Abstract. As mesothelioma risk has begun to decline in the United States, two trends are gaining relative importance. “Legacy” exposures causing this disease are most important in locales having past asbestos industry, shipyards, and/or local distribution of asbestos amphibole-containing material as a result. “Future” exposures are of particular concern in relation to so-called “naturally occurring asbestos” (NOA) areas which include unequivocally asbestiform amphibole. In this paper, Jefferson Parish, Louisiana is used as an example of the first trend, and El Dorado County, California as an example of the second. Available tumor registry, epidemiology, historical and mineralogical data, and lung-retained fibre content are used as indicators of disease and exposure. Jefferson Parish, LA was chosen as the prototype of “legacy” exposures on the basis of historical evidence of asbestos plants with known mesotheliomas in the workforce, known shipyards in the same area, EPA records of distribution of crocidolite-containing scrap to and remediation of over 1400 properties, NIOSH published data on mesothelioma by county, and exposure data including lung-retained fibre analyses in victims, where available. El Dorado, CA was chosen as the prototype of NOA amphibole exposures on the basis of tumor registry data, activity-based EPA sampling data in one area, and lung-retained fibre analyses in area pets, and future risk assessment based on tremolite-specific modelling in Libby, Montana and elsewhere. As expected, the legacy exposure area was high in mesothelioma incidence and mortality. Lung-retained fibre content confirms crocidolite exposures in exposed plant-workers and those exposed to crocidolite-containing scrap, and amosite in shipyard workers. In contrast, to date, cancer registry data in the NOA-amphibole (“future”) county does not show a clear increase in incidence or mortality, but grouped county data from the area show a shift in higher incidence rates to the NOA areas and away from California “legacy” (e.g., shipyard) areas from 1988-2005. EPA active sampling has confirmed excess tremolite/ actinolite fibre(s) in air, although there is debate about its nature and the appropriateness of the area sampled. Lung-retained fibre in local pets shows unequivocally elevated asbestiform tremolite/ actinolite in areas thought to be most affected, but numbers are small. Future risk is expected to rise due to a vastly increased population base coupled with

exposures potentially created by related construction activities. Although legacy exposures are producing smaller numbers of cases with time, they continue to occur at high rates, and new sources of legacy exposure are being discovered in highly localized “hotspots”. Differential exposure sources remain a problem in attribution, but continued remediation seems the best strategy for prevention. In the “future” risk county and surrounding areas, incidence trends are less clear, but again highly localized exposures as opposed to broad areas seem important. Activity-based air sampling; targeted soil samples, and lung-retained fibre analyses may be useful in defining areas of highest future risk and potential prevention.

1. Introduction

Patterns of geographical distribution of mesothelioma cases in the United States were last studied in depth over 20 years ago [1,2]. Authors noted that, with some exceptions, highest concentrations of cases were likely to be noted in counties having either asbestos-using industrial plants, shipyards, or both. Most studies of mesothelioma incidence in the United States have relied on the Surveillance, Epidemiology, and End Results Program (SEER) data, a subset which is incomplete but which also supplies cases for nine jurisdictions [3]. According to this source of information, mesothelioma incidence among U.S. men peaked before the turn of the century and has begun a slow decline [3,4], possibly due to decline of use of commercial amphiboles since the late 1960’s [3].

While the decline is welcome, it brings new challenges for mesothelioma ascertainment. These can be divided into three parts:

- a deficit in the SEER data itself
- a persistence of the “legacy” exposures both in their traditionally known forms (as in continuing risk from past direct and indirect exposures from transformation plants and shipyards) and newly discovered offshoots (as in the distribution of asbestos-containing (AC) scrap from such sites), and
- exposure from mineral deposits not commercially exploited, either directly via disturbance of the material *in situ* or indirectly via transport by wind or water; this is sometimes called *naturally occurring asbestos* (NOA), although the distinction is in lack of present commercial use, not geological occurrence. Past sources of commercial exploitation can become current sources of NOA exposure, or they can occur through weathering or development not specifically aimed at extraction of the minerals, such as construction activities or real-estate development siting.

1.1. Deficits in the SEER data itself.

SEER data is by definition limited to those jurisdictions from which it is derived. Both overestimates and underestimates of mesothelioma incidence nationwide are theoretically possible, depending on the representativeness of the data. It has been suggested that, for example, studies of attributable risks of varying causes of mesothelioma based on the SEER data may have overestimated shipyard, ship-building and ship repair, since the data-set includes the Los Angeles County area (as well as cases and controls from the Veterans Administration). Los Angeles County had a disproportionate share of such activities and 46% of incident cases were attributable to exposures from those sources there, not “directly representative of the whole population of the United States” [5]. The accuracy of diagnosis data within the SEER data has also been questioned, but this incidence data matches national mortality data quite well for 1998-1999 if compared with ICD-10 mortality data for mesothelioma for the same areas [6].

1.2. Persistence of legacy exposures.

Commercial amphibole exposures occurred long after the late 1960's in the United States. For example, crocidolite consumption in the manufacture of products constituted nine per cent of U.S. total asbestos consumption in 1981, 95% of which was in the production of asbestos cement pipe [7]. Amosite consumption in insulation production continued to a lesser degree after 1972, when the U.S. Navy formally discontinued asbestos use (amosite had constituted up to 85% by weight, by specification, of naval ship insulation during World War II [8]). However, exposure to amosite in installed insulation and other products in secondary trades continued (and continues), as amosite by one account was identifiable in the lungs of 82% of all mesothelioma victims analyzed over the last 25 years [9].

An emerging source of exposures to commercial fibre is domestic use of industrial scrap, which unless painstakingly remediated may remain in a neighborhood virtually forever. This has occurred for example in Italy near a crocidolite-using asbestos cement plant, where close examination of exposures of mesothelioma cases identified “the use of AC residuals such as mixing them into the soil to create hard pavement and improve water absorption or applying layers of finely ground AC—rich in asbestos fibres—in the lofts for thermal insulation” [10]. Distribution of crocidolite-containing scrap throughout an entire county by an American cement pipe plant is an example offered in this paper, for Jefferson Parish, Louisiana; a county which included other asbestos product plants and shipyards as well. Exposures from all three “legacy” sources have contributed to the burden of mesothelioma, making it one of the highest-incidence counties in the nation (see “Results”).

1.3. Exposure from mineral deposits not commercially exploited (NOA).

Of the 50 American states, 35 have been identified by the United States Geological Survey (USGS) as containing asbestos occurrences, most of which have not been exploited. These are largely in two areas. The first begins in Eastern Canada and runs down the eastern coastal and inland states; USGS counts 60 former asbestos mines and 331 “Natural asbestos occurrences” in this area, including not only chrysotile but former anthophyllite asbestos mines in Georgia, North Carolina, Virginia, Maryland, Connecticut, and Massachusetts [11]. The second most important belt of occurrences runs from Alaska through British Columbia, Washington State, Oregon and California; as yet, it has not been as well characterized although California was the site of the largest chrysotile mining operations in the western USA and chrysotile was also mined in northern British Columbia. Other occurrences have been identified in the central and “Rocky Mountain” states [12,13]. Most recently, USGS has published tables and maps of NOA in the southwest including Arizona, Utah and Nevada, including information on 113 occurrences, most in Arizona where there are 46 former chrysotile mines, the last of which closed in 1982 [14]. Tremolite, apart from being possibly associated with occurrences of other minerals, was also specifically mined in Utah; tremolite and actinolite are commonly encountered but not well characterized as to whether they are “asbestiform” or “non-asbestiform but fibrous”, a distinction which may lack biological significance [15].

Except for the unusual Zonolite Mountain deposit of mixed asbestiform amphibole at Libby, Montana, which had a very high proportional mortality for mesothelioma among the workforce [16-18] and residents [18] in and near the vermiculite mine located there, there have been no real investigations of NOA mesothelioma causation – or even of the workforces of the over 100 previous asbestos mines. A single exception looked at residential proximity to California asbestos deposits as the independent variable for mesothelioma incidence 1988-97 in the California Cancer Registry, and found a significant relationship [19]. Like all ecologic studies this one was potentially hampered by inadequate occupational and other individual exposure data, including residential proximity itself other than that at time of diagnosis, but the positive results do suggest caution in residential siting. El Dorado County, on the western slope of the Sierras and known to contain deposits of asbestiform tremolite/ actinolite, has been an area of particular concern in this regard and is the county used as the NOA example in this paper.

2. Methods

2.1. Selection of counties and sources of information.

The choices of Jefferson Parish, Louisiana as representative of a “legacy exposure” county and of El Dorado, California, as representative of an “NOA exposure” county were made *a priori* on the basis of familiarity of the authors with these areas. As a first step in seeking out information, state cancer registries in the two areas were examined (although as noted below this proved unsatisfactory in Louisiana). Historical exposure data, including published papers, geological maps, and documentation of exposure in the two areas by regulatory agencies was sought out in general terms, including identification by bibliographic search (e.g. Pubmed). Individual mesothelioma cases were culled from the files of one of us (BWC) for Jefferson Parish; neither of us had a file on a case in El Dorado county, which we regard as an area primarily of future risk rather than past exposure, although certainly exposures may have occurred in the past. Information on potential exposure(s) was obtained from deposition testimony, social security records, medical records, and records of employment where available. Where possible, lung tissue was obtained and analysed as outlined in the following section.

2.2. Lung-retained fibre analysis.

Mesothelioma cases from Jefferson Parish for which lung-retained fibre analysis were performed by one of us (BWC) were analysed according to the methods published for the McGill University laboratory [20-25]. Briefly, lung samples were obtained from paraffin blocks after identification from corresponding stained slides, deparaffinized with filtered xylene, and prepared for analytical electron microscopy following digestion with filtered household bleach followed by oxidation in a low-temperature asher with grid preparation using a carbon replica technique. Fibre identification and counting were performed at a magnification of 13,500X in a Phillips 420TM electron microscope equipped with an energy dispersive spectrometer permitting the capture of X-Ray energy dispersive spectra (EDS) of individual particles. Fibres were defined and counted as having length greater than 5 μm and aspect ratio greater than 3:1. EDS spectra were observed and evaluated online; reference standards for comparison were spectra obtained from similarly prepared grids holding UICC samples of amosite, crocidolite, and chrysotile and a Research Triangle Park sample of tremolite, among others. Fibres were counted in two samples from different parts of lung to a theoretical maximum of sixty fields per sample (detection limit 34.37 fibres / mg dry lung).

For El Dorado county, no mesothelioma cases were available: for exposure assessment cat and dog lungs obtained from local veterinarians were obtained and analysed using both the McGill methods as above and the SUNY lab methods. The latter were similar with respect to sample preparation and fibre identification, but scanning electron microscopy was used at a magnifications of 4000X and 8000X rather than transmission electron microscopy as in previous work from that laboratory [26-28].

3. Results

3.1 Legacy exposures in Jefferson Parish, Louisiana.

The Louisiana Tumor Registry proved not to be a useful source for county-by-county comparisons of mesothelioma rates. This is because that registry groups counties together into regions for some purposes, and therefore Jefferson Parish – the chosen county for this paper – is grouped with Orleans Parish (which includes the city of New Orleans proper) as well as St.-Bernard Parish. The latest figures for the three counties combined nonetheless show the *region* to have the highest age-adjusted (to the 2000 U.S.

population) annual incidence rate in the state at 2.1 per hundred thousand for the five years from 2000-2004, based on 104 recorded cases (69 in white males; 19 in white females), as compared to 1.3 for the state as a whole [29]. The county was not listed as one of the high mesothelioma rate counties in 1987 [1,2], and is not included in SEER data (nor is any county in Louisiana), but the New Orleans “state economic area”, which includes Jefferson Parish, had a “significantly high” SMR for “pleural cancer” (ICD8 code 163.0) among white females for U.S. death certificate data 1968-78, although not for males [2]. Overall, 14 of 174 such economic areas in the US had “significantly high” female pleural cancer mortality, and of these five, including the New Orleans area, had both shipyard(s) and asbestos manufacturing plant(s). At least two of the latter were present in Jefferson Parish; workforces for these were studied by Hughes and Weill [30]. One of the two was the Johns Manville plant, which included a pipe-manufacturing facility which used crocidolite “steadily” in manufacture of “transite” cement pipe. Hughes et al. identified eight mesothelioma cases in workers from this plant, and found further in an internal case-control analysis that mesothelioma was related to proportion of time spent in the pipe area, as well as duration of employment. Although the plant existed from 1928, the pipe plant opened in 1947. According to US EPA and Louisiana Department of Environmental Quality (LDEQ) documents obtained through freedom of information requests, through the 1950’s and 1960’s, in addition to atmospheric pollution from the plants, plant personnel produced an asbestos-containing aggregate which was distributed throughout the communities of the surrounding area (the “Westbank” of the Mississippi River). This contained both chrysotile and crocidolite asbestos, in a proportion varying from 1:3 respectively to 1:1, and determined by testing to be 35% to 45% total asbestos by weight. It was created in a hammer mill and mixed with a filler, usually composed of gypsum, dolomite, or calcite. The asbestos aggregate and filler formed “a concrete-like material when mixed with water and therefore was considered by many local residents to be a concrete substitute for construction purposes” [31]. It was distributed to local residents free of charge, often by pickup or dump trucks. It was first identified as a potential hazard in 1990; then again in 1992 and 1994, but by 1996 it had become friable and was considered an “imminent threat” to public health, with mesothelioma mentioned specifically as a possible outcome from exposures [31]. The material was “located in residential yards and driveways, school playgrounds, around day care centers, and in other areas easily accessed by the public” and “Children were seen playing on driveways composed of friable ACM with toys and basketballs...vehicles were observed creating dust clouds when passing over areas that contained the ACM. All of these routine activities (were) expected to increase ACM friability and dramatically increase human exposures” [31]. In 1996 remediation activities began, and currently over 1400 properties have been remediated; however, a walk-through of the residential areas near the plant in 2008 by one of us (BWC) clearly identified areas without mitigation, including some in the drainage paths from the plant and from dump sites. In 1999, according to NIOSH data, Jefferson Parish had the eleventh-highest age-adjusted mortality rate at 39.9 per million population for U.S. residents age 15 and over, based on six deaths in women and eight in men (the corresponding overall U.S. rate ranged between 11.32 and 11.64 in the four years from 1999-2002) [32]. Recently NIOSH published an up-to-date supplement of this data for the five years from 2000 to 2004, finding 75 deaths from mesothelioma in that time period (age-adjusted rate 42.1 deaths per million, of which 34.7% were female) in Jefferson Parish [33]. This is by far the largest current number of mesothelioma victims in high-rate counties in the USA, exceeding by fifteen-fold for example the five deaths seen in the same time period in Lincoln County, Montana, where the Libby “epidemic” is situated [33].

3.1.1. Total cases identified. Twenty-two Jefferson Parish medicolegal mesothelioma cases (ten female and twelve male) were identified by one of us (BWC) from our files. At least six of the 22 were related; two sets of siblings and one parent and child. All were resident at some time in their lives (most frequently for most of their lives) in Jefferson Parish. All had pathologically verified mesothelioma,

confirmed with immunohistochemistry. All but one were pleural. The peritoneal case was a 39 year old female with no definite history of asbestos exposure. All other cases (12 male and 9 female) were pleural and had a definite history of asbestos exposure including one or more of direct occupational exposure in asbestos manufacturing plant(s) or shipyard(s) in the area; indirect exposures (household or domestic exposure, usually via the laundering of clothes from such workplaces by family members); or environmental exposures through living near asbestos manufacturing plants or at home addresses where asbestos-containing materials had been directly deposited. Some had also attended schools where the ACM scrap was placed in the yards during childhood. Many had suggested possible exposures from multiple sources including two or more of the above, making attribution difficult in some cases.

3.1.2. Abbreviated exposure histories for pleural mesothelioma cases for which lung tissue analysis could not be performed. For 12 of the 21 pleural cases (six men and six women), no lung tissue was available for assessment of retained fibres to aid in exposure assessment. Of these, four were men who worked in shipyards; two for at least twenty years, one in his “college years”, and one before becoming a fireman. The latter recalled exposure to amosite-containing insulation and many other asbestos-containing products and also had a crocidolite scrap driveway as a child. A fifth man had crocidolite-containing scrap material deposited at his residence in childhood; a sixth had such material in the neighborhood but could not recall his childhood address. Both of the latter also claimed chrysotile exposure in automotive brake work. Of the six women with no lung fibre analysis five had crocidolite-containing scrap deposited on their property as children, and one of the five lived approximately three hundred feet from the pipe plant for twenty years. Four laundered clothes of fathers, husbands and/or sons who worked at one time either in the asbestos manufacturing plants in the area, in shipyards, or in both.

3.1.3. Cases identified with previous fibre analysis or with lung tissue available. Lung tissue had been analysed previously in other laboratories in two cases. One was a 66 year old woman who had a crocidolite-containing scrap driveway as a child and one crocidolite-cored asbestos body and two tremolite fibres were identified from lung tissue; the other was a shipyard electrician who had an unspecified number of amosite fibres identified in his lung tissue with relatively low (4000 amosite fibres per gram wet lung) concentrations. Close examination of the methods in the latter case however suggest this result may not be reliable, as the analyst had no past experience with the technique, no description of methods and no published or unpublished control values. Samples were available for our own analysis and provided in seven cases. Results for these cases are shown in Table 1.

Table 1. Jefferson Parish mesothelioma cases with lung-retained fibre analysis^{a,b}.

Age, Sex Latency	Primary exposure	Other exposures	Crocidolite	Amosite	Other ^c
49 M; 49 yrs	Residential ^d	Barges (no insulation)	344, 344	n.d. ^e , n.d.	n.d., 34 (Ch) 2640 (AB)
64 M; 42 yrs	Shipyards electrician	Residential	n.d.	3093, 2690	Fibres n.d. by TEM; 15,360 (AB)
52 F; 52 yrs	Residential	none	172, 206	n.d.	Fibres n.d. by TEM; 1480 (AB)
57 M; 52 yrs	Residential	Sales, home improvement	n.d.	n.d.	Fibres n.d. by TEM; AB n.d. by PCOM
60 F; 54 yrs	Residential	Domestic ^f	309, 109	n.d.	n.d., 69 (Ch) 8000 (AB)
75 M; 58 yrs	Occupational- Pipe plant	Occupational- Chem. Plant	722, 1134	69, 137	34, n.d. (Ch); n.d., 69 (T) 24,000 (AB)
57 M; 52 yrs	Residential	Shipyards, < 1 yr.	1134, 825	n.d.	No other fibres by TEM; 2933 (AB)

^a Fibres > 5 micrometers per mg dry lung; aspect ratio > 3:1; detection limit 34 f/ mg (i.e. 1 fibre = 34 f/mg).

^b Where two values are given, two separate analyses were performed from two parts of lung.

^c (Ch) = chrysotile (background = 60-80 [15, 20-22]); (T) = tremolite (background = 40-60[15,20-22]); (AB) = asbestos bodies by phase-contrast optical microscopy per gram dry lung (background < 1000).

^d Residential = crocidolite-containing scrap at residence in childhood.

^e n.d. = none detected

^f Alleged household exposure via laundering of clothes of relative who worked in shipyard < 2 yrs

3.2. Assessment of NOA exposures in El Dorado County, California

3.2.1. Previous work by others. The possibility of tremolite/ actinolite asbestos exposures in the then thinly-populated county of El Dorado, east of California’s capital Sacramento, first came on the national scene with a series of newspaper articles by Chris Bowman of the Sacramento Bee. Mr. Bowman was following up on the dilemma of a local citizen who had felt forced to leave his home in the county because of the newly-discovered risk. It has long been known that such fibre was present; it is clearly indicated for example on the 1970 state geological maps used by Pan et al. [19] in their assessment of mesothelioma risk and proximity to naturally occurring asbestos deposits. In an intraperitoneal animal experiment designed to highlight differences in risk between “asbestiform” and “nonasbestiform” tremolite/ actinolite (the latter has not been regulated as asbestos since 1992 and there is debate about health effects of the very wide range of fibres and particles covered by the definition[15]), the asbestiform fibre found to produce mesothelioma most rapidly and consistently was one from a source near this area of California [34]. Citizen concern in the area sparked regulatory agency attention, with an activity-based sampling regimen applied by US EPA in a study performed in 2005 [35]. During the study, EPA technical personnel simulated recreational activities at schools and a park, including cycling, team sports and running. Personal air samplers were worn during the activities and dust was collected from breathing zones to

represent potential exposures to both children and adults. Several protocols were used in electron microscopic fibre counts, including modified ISO 10312; “Phase Contrast Microscopy Equivalent” (PCME) counts of fibers longer than 5 micrometers, with aspect ratios greater than 3:1 (to conform to measures used in exposure assessment in historical epidemiology studies using phase contrast optical microscopy). Results were summarized by EPA: “U.S. EPA found asbestos fibers in almost all El Dorado Hills air samples, including those collected nearby, but outside the area of activity. In general, personal asbestos exposures from simulated sports and play activities were significantly elevated over levels observed in the nearby asbestos air samples taken outside the area of activity. The dominant asbestos fiber type detected was amphibole, which is considered to be more toxic than chrysotile” [35]. There was some debate between EPA, an industry lobbying group, and some elements in the El Dorado community governance about the appropriateness of counting methods, and the degree to which identified amphiboles were asbestiform (as opposed to “cleavage fragments”); leading to the US Geological Survey conducting their own investigation in the area [36]. They concluded that both types of “fiber” were present at different sites, and that “Based on aspect ratio data of the less than 3 um diameter particles, the morphologies of the amphiboles in the El Dorado Hills area are intermediate between what might generally be considered a population of commercial-grade asbestos particles and a population of cleavage fragments, produced by milling of massive amphibole” [35]. They stressed further that measurement, not health effects evaluation of any population of fibres, is the province of mineralogists and allied scientists: “It is the obligation of the analytical and mineralogical communities to provide accurate, unbiased, and scientifically sound information to the health and regulatory communities so that appropriate and informed, health-related policy and regulatory decisions can be made” [36].

This series of events left many in the community confused, divided and angry. Some saw a playing down of risk based on obscure mineralogical criteria with no proven health implications. Conversely, others saw unfair singling out of their community (California being well-known to contain much serpentine rock – indeed, it is the “state rock” – often home to asbestos deposits which are largely chrysotile), even though the instigation and emphasis of the investigations had always been on the basis of the presence of amphiboles, and any arguments between scientists had had no relationship to chrysotile asbestos). Although further studies had been planned, including government-sponsored “expert” conferences and risk assessments, none were performed, leaving the situation in limbo.

3.2.2. California Cancer Registry Data. We looked at figures in the California Cancer Registry using their online tool, which allows county-by-county comparisons for any time period demarcated by years between 1988 and 2005. Given the small population at risk, long latency for mesothelioma and time window we expected this might not be sufficient for detecting trends. Mesothelioma (ICD-10) was not coded but pleural cancer was. In fact, there were 33 cases registered for “Pleural Cancer” from 1988-2004 for an age-adjusted rate per 100,000 of 1.36; seventh highest in the state. Also of interest, two of the six higher-incidence counties (sometimes grouped) were immediately adjacent and also on the Western Slope of the Sierra, where tremolite/ actinolite deposits are scattered: Mariposa – Toulomne (30 cases; rate 1.93) and Alpine - Amador – Calaveras (23 cases; rate 1.86). For comparison purposes, Los Angeles County, included as noted above in SEER data and having in the past 46% of cases attributable to exposure from shipyards [2] had a rate of only 0.85. However, this was based on 1044 cases 1988-2004, with a “population at risk” two orders of magnitude higher. Nevertheless, 95% CI on rates did not overlap, showing a significantly increased mesothelioma rate for El Dorado County vs. Los Angeles County (and for the other Western Slope counties) over this time period (difficulties with interpretation of this type of comparison are evident and are discussed later).

3.2.3. *Lung-retained fibre analysis.* It has not been possible to obtain lung samples from mesothelioma victims – or from hospitals, coroners’ offices, or any other source – in El Dorado County, despite four years of efforts in that direction. In the interim, we elected to begin to collect as possible pets (cats and, preferably, dogs) who died of natural causes in county. These were provided by concerned citizens and lungs were obtained *in toto* at post-mortem by local veterinarians and supplied to our laboratories for analysis. To date, we have received lung samples from two cats and four dogs; five have been analysed in both laboratories, as reported here; analysis is not complete in the McGill laboratory for the final dog. Results for the from both McGill and SUNY laboratories to date for tremolite/ actinolite concentrations at two fibre lengths are shown in Table 2.

Table 2: Lung fibre concentrations in El Dorado County pets from two laboratories^a:
 Tremolite/ actinolite fibres/ gram dry lung, aspect ratio > 3:1

ANIMAL	Exposure	SUNY Lab > 5 um length	McGill Lab > 5 um length	SUNY Lab > 10 um length	McGill Lab > 10 um length
Cat 1	none	0	0	0	0
Cat 2	9 years, indoors	86,000	157,000	86,000	157,000
Dog 1	> 2 years	1,250,000	566,500	192,000	412,000
Dog 2	> 8 years	9,162,000	928,000	2,030,600	928,000
Dog 3	unknown	186,000	204,000	72,000	47,500
Dog 4	unknown	961,000	-	448,000	-

^aMcGill Laboratory: each value is the mean of two samples; analysis by Transmission Electron Microscopy (TEM) ; SUNY (State University of New York) Laboratory: each value is the mean of two to three samples; analysis by Scanning Electron Microscopy (SEM). Both laboratories used similar sample preparation and fibre identification for tremolite/ actinolite (by EDS) methodology.

Of the six animals shown, the first (Cat 1) did not live in an area known to contain tremolite/ actinolite. The second cat did, but (like most cats) spent most of its life indoors. Dogs 1 and 2 both lived in “exposed” areas but as shown there was greater lung concentration of tremolite/ actinolite shown in both laboratories for the dog with longer residence time. For the third and fourth dogs we have not yet obtained “residential histories”, and analysis is incomplete. Other fibers were also found but in small numbers and concentrations except for Dog 3 in the McGill Laboratory; this dog had 204,000 fibres (mean of two counts from two portions of lung based on eight fibres seen) tremolite/ actinolite with mean length 10.4 micrometers but chrysotile concentration was, unlike in the other cases, very high at mean over 2.5 million fibres per gram dry lung and very long with mean fibre length over 13 micrometres. However, this was not replicated in the SUNY laboratory in which no chrysotile was seen at a detection limit varying between 7000 and 20,000 fibres per mg dry lung.

4. Discussion

Results in these two counties show two very different patterns relating to exposure and mesothelioma risk. Each presents scientific and medical dilemmas; each can be aided by obtaining accurate statistics on mesothelioma incidence and mortality, and ideally, lung-retained fibre analysis (where possible). In this section we discuss the central dilemmas for legacy exposures and for future risk from NOA exposures and suggest ways in which addressing them may be improved, as well as current deficiencies both in the available data from these counties and in our own analysis. Finally, addressing the different problems for these two situations has some common – and common-sense – solutions.

4.1. Legacy exposures

Although asbestos use (consumption) in the USA peaked in 1973 [37] and mesothelioma incidence is said based on SEER data to have peaked in the 1990's [3,4] U.S. mesothelioma *mortality* remains approximately flat at 2500 cases per year for the most recently available (1999-2002) National Center for Health Statistics multiple cause-of-death data (ICD-10 data). As may be seen in this report, latency remains very long, although there is some indication that the linear increase with time from first exposure after approximately 20 years flattens out after 50 years from first exposure [38]. It is therefore not surprising that most cases continue to be due to legacy exposures; indeed on the basis of consumption figures alone incidence would be expected to keep rising for another decade. New trends have appeared in addition to the known exposures, which in the USA were maximal in counties that had asbestos manufacturing plants and shipyards. Some legacy exposures are due to secondary exposure from the latter, both through past neighborhood and domestic exposures and past and continuing exposure from material distributed from manufacturing plants, such as that described here for Jefferson County, Louisiana. The exposure profile overall in such a neighborhood can therefore historically be quite complex, leading to concomitant complexity in attribution. The latter is relatively easy to estimate in a population by, for example, type of exposure or occupation. Attribution of the *individual case*, however, sometimes called “specific causation”, remains a problem. One approach has been to apply what we know about *population* risks – namely, that they are related to differential fibre potency [39] and to the third to the fourth power of time from first exposure [40]. One model has been constructed to apply dose reconstruction for these two powerful factors in *general causation* to specific causation [41]. While this has some appeal, it is controversial. For one of us (BWC) it lacks biological rationale for the individual case, since it does not seem possible given the accepted tenets of carcinogenesis that in the individual case a large number of exposures could simultaneously, or even in sequence, have been causal. On the other hand, experts disagree on this matter, and indeed that includes the two authors of this paper. One of us (JLA) feels it is, conversely, quite biologically plausible that ALL exposures contribute to the resultant mesothelioma, and that it is not currently possible to exclude any one documented exposure completely, *if* had that one lesser exposure been the only one, there would be no argument that it was sufficient and the only cause.

Whichever view is taken, this leaves those concerned with compensation for the individual case with a dilemma – when more than one exposure has *occurred*, how does one decide biologically which exposure(s) is (or are) causal? In many jurisdictions such a decision must be made, and some US Appeal Courts do not allow “expert” opinions with wordings such as “each and every exposure contributed to...” or “each and every breath of asbestos-containing air was a cause of...” the disease.

While it appears sensible, where possible, to assign attribution to the most important exposure (in terms of dose or some surrogate for dose, with the above-noted corrections for fibre type and for time from first exposure), it is not always possible. Evidently, if science cannot determine which exposure is the one which *was* causal in the individual case, and multiple possibilities exist, there needs to be a balance between fairness to the individual with disease and fairness to those, if any, deemed “responsible” for the exposures that constitute those possibilities. Where available, lung-retained fibre analysis can provide one component of the solution to this difficulty. This is evident in the Jefferson Parish cases having unequivocal lung-retained fibre results in which it is clear either that a professional (for example, amosite from shipyard insulation or crocidolite from cement pipe manufacture) or residential (for example, from crocidolite-containing scrap on a person's property to which that person was exposed in childhood) exposure was most significant. Arguments may be raised that rapid differential clearance may cause an exposure to (for example) chrysotile to “disappear”; conversely however it is just this rapid clearance that has often been raised as the explanation for the wide differences in risk between fibre types

[3, 39, 41]. Of course, lung tissue is in any case not always available from medical procedures such as diagnostic lung biopsy, therapeutic pleuropneumectomy, or autopsy requested by relatives.

Better cancer registries – or preferably, a dedicated mesothelioma registry of the type available in parts of France [42] and in the past (1980-85) in Australia [43] – could contribute as well, although their main contribution would be to a better ascertainment, diagnosis, and treatment of the disease. Unfortunately the Australian example with the demise of the quality of the registry with defunding after 1985 [43] indicates that obtaining adequate funding for this endeavour will not be a simple matter. Pending legislation in the US Congress has suggested funding a Registry there, but the details remain vague.

No matter what solution is suggested, there will inevitably be controversy associated with it, as fixing blame on a maximum number of potential parties increases potential rewards in tort litigation both for patients and lawyers, while also spreading financial risk more thinly among defendants.

4.2. Future risk from NOA exposures.

As with legacy exposures, exposures such as NOA, which create *future* risk, may be aided in improved assessment via cancer registries and by better exposure assessment techniques which adequately address both current and past exposures, including lung-retained fibre analysis where possible, as long as performance of the latter is not made an excuse for inaction. The latter is self-evident, and can easily be achieved through acquisition of lung samples from previously taken therapeutic lung biopsies and resections, routine autopsies from hospitals, or from coroners' departments. In addition, there are many already-analyzed series of residents of given communities which may be found in the literature and used for this purpose. Two examples of autopsy series used for exposure assessment via lung-retained fibre analysis are our analysis of the lungs of children for US EPA [44] and our assessment of Canadian background lung asbestos values by obtaining right upper lobe samples from coroners in nine of the ten provinces and both Territories [45]. Examples from a wide range of patients from many states were provided in both study subjects and controls for exposure assessment related to the man-made mineral fibre industry [46]. Direct assessment in relation to proximity to asbestos sources has shown that lung content varies inversely with distance from chrysotile mines and directly with duration lived within ten km of such mines [15,20,21]. All of the latter studies were funded through peer review by public agencies in Canada and the USA, so there is every reason to believe the same could be achieved for studies relating to proximity to NOA.

4.2.1. Translating NOA exposure assessment to risk assessment for mesothelioma. While better cancer registries will provide better characterization of where disease occurs, and lung-retained fibre analysis (as well as the type of activity-based air sampling practiced by US EPA in El Dorado Hills, California [35]) will help in exposure assessment, linking the two in risk assessment is no simple matter. Cancer registries are by definition ecological in nature, “counting cases” in given areas and comparing them to national or other rates. They cannot produce individual risk data, and the same deficiency is evident for studies such as that of Pan et al. which ultimately rely on cancer registries for their disease data [19]. The confounding effect of legacy exposures, particularly those related to occupation which still cause the highest proportion of cases nation- and world-wide, are a particular problem. Only dedicated studies which provide individual measures of both disease and exposure are likely to provide definitive answers.

4.3. “Current” legacy exposures and NOA exposures: A common problem.

As past occupational exposures become an increasingly less important source of mesothelioma risk with increasing time, current NOA exposures and legacy exposures which are due to unremediated waste or scrap left over from the past will become the source of an increasing proportion of mesothelioma risk. Although their origins are quite different, their effects are likely to be similar, depending on exposure

patterns. The most important task we face is to *identify* them, as has been the case in Jefferson Parish, Louisiana and El Dorado County (and the rest of the Western Slope of the Sierras). Once identified however further tasks await. Once found, sources must be characterized; some will be serious and require remediation or other corrective measures. Those which provide disease risk are of particular concern, but we should not wait until disease has been established to begin to prevent exposures. Epidemiology is a useful tool for identifying past “epidemics”, whether of infectious diseases or cancers caused by toxic materials. But we cannot wait for the comfort of epidemiological proof where exposures we know to be analogous to those which have produced disease in the past exist. Once identified, both legacy exposures and NOA exposures must be eliminated as possible causes of future disease.

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Competing Interests

Drs. Case and Abraham have acted as expert witnesses for law firms representing defendants and/ or plaintiffs in asbestos litigation and/or compensation board proceedings in the United States and Canada, and have been paid and unpaid consultants to regulatory agencies and compensation boards in North America. Both have also provided unpaid assistance to community groups and residents having concerns with the types of asbestos exposure discussed in this paper, including residents of El Dorado County, California.

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