Fiber Width as a Determinant of Mesothelioma Induction and Threshold—Bolivian Crocidolite: Epidemiological Evidence from Bolivia—Mesothelioma Demography and Exposure Pathways

E. Ilgren, R. Ramirez, E. Claros, P. Fernandez, R. Guardia, J. Dalenz, Y. Kamiya and J. Hoskins

Affiliations: 1Consultant Scientist and Physician, Bryn Mawr, PA, USA; 2Consulting Engineer, Cochabamba, Bolivia; 3Department of Pathology, Cancer Hospital, Santa Cruz, Bolivia; 4Department of Pathology, San Simeon Medical College, Cochabamba, Bolivia; 5Department of Pathology, UMSA, La Paz, Bolivia; 6Consultant Geo-Political Scientist, Santa Cruz, Bolivia and 7Consultant Toxicologist, Haslemere, Surrey, UK

ABSTRACT

Crocidolite is a well known causative agent for mesothelioma. Studies have shown that the pathogenicity of the fiber from different mines varies considerably and it has been postulated the parameter that appears most likely to account for this variation is fiber width. Epidemiological studies have shown that ‘thin’ fibers from mining areas of Western Australia and the Cape Province, in South Africa are associated with a high mesothelioma risk while exposure to ‘thick’ asbestiform amphibole fiber of the same fiber type are associated with little or no mesothelioma risk. This study is concerned with ‘thick’ Bolivian crocidolite but similar findings also probably explain the paucity of mesotheliomas in the Finnish anthophyllite, South African amosite and African Transvaal crocidolite mines. The findings from the present study suggest the incidence of mesothelioma in the three major cities of Bolivia is not significantly elevated above background even though Bolivian crocidolite has been used for the past 60 years commercially and residentially in all three cities. Although some cases of mesothelioma may have been missed due to a failure to reach hospital or a shortened natural lifespan, mesothelioma generally occurs after the age of 50, we cannot tell precisely the extent to which these were confounding. We suggest the most likely explanation for the lack of mesotheliomas despite the large populations at risk from the long and extensive residential and commercial use of crocidolite containing products, is related to an increased fiber width distribution and a concomitant reduction in the ‘Stanton fiber size’ fraction.

Keywords: Bolivian crocidolite, mesothelioma, fiber width, epidemiology, demography

Correspondence: Dr. E.B. Ilgren, MD, Suite No 503, 830 Montgomery Avenue, Bryn Mawr, PA, USA. Tel: 001 610 624 1510; e-mail: dredilgren@aol.com

INTRODUCTION

The evidence for a threshold for asbestos related mesothelioma in animals and humans has been reviewed by Ilgren & Browne. “Threshold for tumor induction refers to an upper cumulative dose of potential carcinogen to which an organism may be exposed without observing tumor formation within the lifetime following that exposure”. The dose required to reach such a threshold is measured not just in terms of fiber concentration but also fiber size. This is because fiber size is a well recognized determinant of mesothelioma induction both for length and width.

The fiber size fractions most potent for mesothelioma induction, by length and width, are those referred to as ‘Stanton sized’ fibers. These are greater than 8 μm in length and less than 0.25 μm in width. Almost certainly every dust cloud of asbestiform amphibole fibers contain some Stanton size fibers. Exposure to those able to cause mesothelioma contain enough to reach a mesothelioma ‘threshold’. An exposure to a ‘wide’ amphibole asbestos fiber refers to the width that predominates in the dust cloud. Thus, discussion of fiber width is directly related to the issue of mesothelioma threshold. This is why both are discussed in this report.

Confirmation of the role of fiber width for mesothelioma induction should ideally rest upon an epidemiological comparison. ‘Thin’ fibers associated with a high mesothelioma risk should thus be compared with ‘thick’ asbestiform amphibole fiber exposures of the same fiber type where the latter are associated with little or no mesothelioma risk.

Crocidolite appears to be the only fiber type amenable to such a comparative analysis. In a 1985 study, Shedd, from the US Bureau of Mines, examined the fiber dimensions of crocidolites from the world’s four crocidolite mining regions and found:

There were measurable morphological differences between crocidolite fibers that correlate with the high reported incidence of mesothelioma in miners and mill employees in the Cape Province of South Africa (Cape SA) and Western Australia (WA), as compared with little or no
reported incidence of this cancer in the Transvaal Province of South Africa or Bolivia. ... Crocidolites from Western Australia and the Cape Province having more thin fibers than crocidolites from Bolivia and the Transvaal Province.

Shedd\textsuperscript{8} noted Cape SA (81\%) and WA (67\%–83\%) crocidolites contained much higher percentages of Stanton sized fibers than those from the Transvaal (45\%–53\%) and Bolivia (18\%). Unfortunately, detailed epidemiological study of Transvaal crocidolite workers, despite the failure to note a mesothelioma excess in earlier reports,\textsuperscript{9,10} could not be extended due to problems attributable to tracing and follow up.

As an opportunity arose to examine the Bolivian crocidolite industry first hand in 2008, we attempted to assess the potential for this fiber to produce mesothelioma following occupational and residential exposure. We have therefore spent the last three years gathering information on the patterns of mesothelioma found in the three largest cities of Bolivia and on the sources and types of exposures to Bolivian crocidolite experienced over the last 70 years since the industry first began. One difficulty encountered during this study was the paucity of company records available including product information. In consequence we have had to rely on personal recollections for some of the background information.

**Epidemiological Studies of Bolivia Crocidolite and Mesothelioma**

Shedd (1985)\textsuperscript{8} cited Ross (1981)\textsuperscript{11} regarding the lack of reports of mesothelioma in the Bolivian crocidolite mining areas based on Ross’ failure (personal communication, 1994) to find such reports in the literature. He noted:

While the incidence of mesothelioma is reported to be significantly high in the crocidolite mining areas of Western Australia and the Cape Province, ... no reports have been found of mesothelioma associated with the crocidolite mining region of Bolivia.

Although this remains true today, no epidemiological studies of the Bolivian crocidolite industry have ever been done nor have the patterns of mesothelioma demography in different parts of Bolivia been studied. We have investigated this issue over the last three years to identify the various exposure sources to Bolivian crocidolite from mining, milling, end product manufacturing and distribution in relation to mesothelioma induction.

The scale of the mining and milling of crocidolite in Bolivia has been small since its inception with only a single mining operator and processor: SISAM SRL.\textsuperscript{12} So whilst the mining of Bolivian crocidolite began in the 1940’s, it never involved more than a handful of workers at any one time partly because the superficial position of the fiber on the mine site obviated the need for dynamite or drilling, the activities were intermittent partly to accommodate the rainy season, and the humid conditions of the jungle mine site kept the dust levels very low. Similarly, the milling of Bolivian crocidolite took place largely at one plant from 1950 to the present time located in the city of Cochabamba. The plant workforce was small (n < 20) and worker turnover was generally high. In 1989, for example, 40 employees worked in the operations sector: mining and transportation of which five were permanent workers. During the low season, these five workers worked in Cochabamba servicing and repairing the equipment. Therefore, neither the mining nor the milling workforces are amenable to epidemiological analysis. In fact little is known of the health of these workers though we understand no mesotheliomas were ever recorded (Ramirez, 2009; Fibrolit 2011, personal communications).

Given these limitations, we decided to examine the demographic patterns of mesothelioma in the populations of the three largest cities in Bolivia where residential and commercial exposure to in-place Bolivian crocidolite containing products has taken place for more than 60 years. More details on the nature, production and distribution of these products both inside and outside of Bolivia are given below in the ‘Discussion’. Their use has been considerable and has consisted mainly of roof tiles, shingles, water tanks, and boiler insulation. For example, based on data provided to us through discussions with the Director of the company (Fibrolit, 2011, personal commun.), approximately 2.5 million kg of Bolivian crocidolite would have been used in the roof tiles in the city of Cochabamba alone. He noted that, historically, shingles and tiles contained up to 30% crocidolite (30 years or more ago). Moreover, the products: roof tiles, shingles and water tanks were less dense and dustier than those produced today.

It had been noticed that the application and repair of the tiles and shingles, particularly when cut to size before being fit to buildings, created significant dust levels (van Orden, 2011 personal communication). In addition, in-place weathering of these crocidolite containing tiles will also release fibers into the general residential environment. This latter fiber erosion from weathered asbestos cement cladding has been demonstrated by various workers to take place through a surface weathering process “whereby the external surfaces are depleted of cement binder to leave loosely bound, asbestos-rich layers on cladding surfaces”.\textsuperscript{13} The process appears to become severe after 20 years or more of exposure particularly for roofing materials. Released fibers were generally found to be free of attached particles and to be present as straight needle fibers in greater proportions for products containing amphiboles. Campopianpo et al. said that “The high quantity of asbestos fibers found in the material gathered from the gutters (due to the decay of asbestos cement roofs) is testimony to the fact that a slow and continued release of asbestos fibers takes place from the material. In these cases, the biggest problem is the re-uptake of such fibers in the environment”.\textsuperscript{14} Passive air sampling and lung burden study of residents from the three cities that are the subject of this study is in progress to examine the release potential of such in-place materials further. This will be published when complete.
Clearly if Bolivian crocidolite was as toxic as many say, clusters of mesothelioma should have been seen after six decades of extensive residential and commercial use. However, as described below, none has been found and the number of mesotheliomas observed to date does not exceed background.

**THE DEMOGRAPHY OF MESOTHELIOMA IN BOLIVIA**

Bolivia is a country of approximately nine million people. The three largest cities are Santa Cruz (ca 1.5 million), La Paz (1.2 million) and Cochabamba (700 000) (Table 1). Since there is no national cancer registry to which all mesothelioma cases are sent, the assistance of various senior Bolivian pathologists, clinicians and other cancer experts was enlisted in an attempt to determine the demography of mesothelioma. This was done through senior pathologists in each of the three cities who in turn consulted with their clinical colleagues at the major hospitals in their respective regions for cases reported either as ‘mesothelioma’ or ‘?mesothelioma’ in addition to reviewing their own hospital files. The findings of these efforts are as follows:

**Cochabamba**

Cochabamba is located in central Bolivia (Figure 1) at an altitude of 2500 m. It was founded in 1574. It presently has a population of ca one million largely located in an arid valley surrounded by mountains ca 3500 -4000 m in height. Despite its aridity, it is fed by several rivers and a two month rainy season which along with a temperate climate accounts for Cochabamba’s reputation as the ‘bread basket’ of Bolivia. Indeed, in the height of the 17th century silver boom, the Cochabamba valley became the primary source of food for the silver miners in Potosi. By the mid 19th century, Cochabamba reassumed its position as the nation’s granary. As mining shifted away from Potosi to the southwest, Cochabamba and theatres there. He also had had a biopsy in Italy which ‘shingles’, whose family had owned a factory and built hotels and their work histories were not available. He also knew of two cases of peritoneal mesothelioma. According to Dr. Zabala, the latter were always in association with asbestosis but their work histories were not available. He also knew of two cases of pleural mesothelioma. One case was in a 32-year-old man who worked in La Paz and Cochabamba with ‘shingles’, whose family had owned a factory and built hotels and theatres there. He also had had a biopsy in Italy which suggests he may have lived and worked outside of Bolivia. The other occurred in an ex manager of the Duralit plant that processed Brazilian chrysotile and may also have used Cape blue asbestos early in its history for short periods of time.

Dr. Acosta, the senior pathologist at the GI hospital a major referral center for the City and Province of Cochabamba and the provinces of Beni and Oruro, said he saw one peritoneal mesothelioma in a 40-year-old man in 1979. However, he also said in his 35 years at the hospital he saw very few pleural mesotheliomas.

**La Paz**

La Paz, founded in 1548 following major gold finds is located at 3650 m making it the highest capital city in the world (Figure 1). It is situated in a ‘bowl’ surrounded by the Altiplano (a plain 320 km long at 4000 m) and peaks up to 6500 meters. While Sucre is the judicial capital La Paz is the de facto capital of Bolivia where the government executive and legislature work. It is the second largest city in the country and the center for commerce, finance and industry. Some two-thirds of Bolivia’s manufacturing is located in ‘El Alto’ a

---

**Table 1.** Census Population Data by Department and Geographical Area for 1950, 1976, 1992 and 2001 for Bolivia

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolivia</td>
<td>2,704,165</td>
<td>4,613,486</td>
<td>6,420,792</td>
<td>8,274,325</td>
</tr>
<tr>
<td>Urban area</td>
<td>708,568</td>
<td>1,925,840</td>
<td>3,094,346</td>
<td>5,105,230</td>
</tr>
<tr>
<td>Rural area</td>
<td>1,995,597</td>
<td>2,687,646</td>
<td>3,226,456</td>
<td>3,169,095</td>
</tr>
<tr>
<td>La Paz</td>
<td>854,079</td>
<td>1,465,078</td>
<td>1,900,786</td>
<td>2,350,466</td>
</tr>
<tr>
<td>Urban area</td>
<td>292,507</td>
<td>667,126</td>
<td>1,193,821</td>
<td>1,552,146</td>
</tr>
<tr>
<td>Rural area</td>
<td>561,572</td>
<td>767,815</td>
<td>706,965</td>
<td>798,320</td>
</tr>
<tr>
<td>Cochabamba</td>
<td>452,145</td>
<td>720,952</td>
<td>1,110,205</td>
<td>1,455,711</td>
</tr>
<tr>
<td>Urban area</td>
<td>105,486</td>
<td>272,100</td>
<td>586,188</td>
<td>859,409</td>
</tr>
<tr>
<td>Rural area</td>
<td>346,659</td>
<td>448,852</td>
<td>530,017</td>
<td>599,302</td>
</tr>
<tr>
<td>Santa Cruz</td>
<td>244,658</td>
<td>710,724</td>
<td>1,364,389</td>
<td>2,029,471</td>
</tr>
<tr>
<td>Urban area</td>
<td>64,710</td>
<td>374,605</td>
<td>982,396</td>
<td>1,545,648</td>
</tr>
<tr>
<td>Rural area</td>
<td>179,948</td>
<td>336,119</td>
<td>381,993</td>
<td>483,823</td>
</tr>
</tbody>
</table>

satellite city of nearly one million people which is an
extension of urban La Paz with an ongoing influx of
immigrants from other parts of the country.

Prof Jaime Rios Dalenz, the current President of the Bolivian
division of the International Academy of Pathology trained at
Temple University Hospital, Philadelphia, IARC/WHO in
Lyon, France, and the National Hospital in London. He is a
leading senior pathologist in Bolivia and Director of Pathol-
yogy at University Mayor San Andres in La Paz and conducted
the cancer case accession for two time periods, 1978-1982
and 1988-1992. The findings of the case accession including
the incidence of pleural and peritoneal tumors have been
published in the book by Dalenz: "El Cancer en La Paz,
Bolivia. Aspectos Epidemiologicos y de Patologia Geogra-
frica". The case accession was based upon surveys of the
populations of La Paz and El Alto by the Cancer Registry of La
Paz which was established by Professor Dalenz with the
assistance and cooperation of the International Cancer
Research Agency, the State University of Louisiana, and the
Pan American Health Organization. Briefly, medical centers
were visited periodically by the survey group and the medical
records were reviewed weekly. The patient’s age, sex, health
center, origin, primary location, diagnosis, date of diagnosis
(la forma de diagnostic) and the ICD code were entered on
the Registry database. Diagnoses were based on death
certificates using the ninth edition of the International
Classification of Oncology Diseases (CIE-O in Spanish). The
number studied histologically was not given.

The 1978-1982 Survey

The 1978-1982 survey was conducted in cooperation with
the State University of Louisiana during the first three years,
and the Pan-American Health Organization for the last two
years of the survey. Dr. Pelayo Correa from Louisiana State
University and William Haenszel from the Illinois Cancer
Council collaborated on the work during this time period.
The rates of cancer incidence by sex, adjusted to the
population, in its different locations and by 100 000 people,
were described. Rates by age group in the archives of the Registry in the Colegio Médico de Bolivia, were also obtained according to population. All the patients with cancer admitted to the hospitals, clinics and institutes were registered with their medical records. All medical data from other institutes, laboratories and death certificates in those cases confirmed histologically were also entered into the registry. The majority of cases were histologically confirmed. The data in Table 2, from Dalenz, indicate that the incidence of pleural and peritoneal cancers in La Paz from 1978 to 1982 did not exceed population adjusted rates:

The 1988 and 1992 Survey

The second cancer survey conducted between 1988 and 1992 was conducted with the technical and economic assistance of IARC/WHO under the supervision of Dr. D.M. Parkin, Chief of the Descriptive Epidemiology Unit. The data from 1988 to 1992 in Table 3 also demonstrate no mesothelioma excess for either site in either sex.

Santa Cruz

Santa Cruz de la Sierra is the largest and most populous city of Bolivia and the capital of the department of Santa Cruz. Located in the eastern lowlands at 416 m above sea level, it enjoys a semi-tropical climate all year round. Its vibrant economy makes it the most important commercial and industrial hub in Bolivia (Figure 1). It was founded in 1561 but was relatively cut off from the rest of the country until a major highway link with other major centers was completed in 1954. Tropical agriculture flourished after a railway line to Brazil was also opened in the mid 1950’s whereupon the city grew prosperously producing crops such as oranges, sugar cane, bananas and coffee. Dr. Edith Claros Mercado, formerly chief of pathology of the Cancer Hospital in Santa Cruz, has practiced pathology in Santa Cruz for the last thirty years. She oversaw the search of the diagnostic archives of the four major hospitals in Santa Cruz: the Instituto Oncolójico del Oriente Boliviano (IOOB), the Caja Nacional de salud (CNS), the Hospital de la Caja Petrolera de Salud, the private Laboratorio ONCOS and the Hospital Japonés de Santa Cruz; for any diagnostic entries that stated ‘mesothelioma’ or ‘mesothelioma’ for the last 10 years. The senior pulmonologists: Dr. Alfredo Ajata; Dr. Jorge Antonio-Mendez; Dr. Ronald Arce; Dr. Roberto Paz and radiologists conducted the searches and interviewed clinicians and radiologists at the various hospitals in Santa Cruz. In addition help was given by an assistant pathologist, Dr. Carolina Henestrosa and three pathology residents.

Thirteen cases had the diagnosis of mesothelioma or ‘mesothelioma’ somewhere in their case records. The details thus provided on the 13 cases are shown in Table 4. After consideration of the strength of the diagnoses for these cases we believe at most three are true mesotheliomas with any possible causal association with asbestos exposure. The rarity of the diagnosis was consistent with Dr. Claros’ overall impression that these tumors were very rarely found in Santa Cruz.

DISCUSSION

Our findings suggest the incidence of mesothelioma in the three major cities of Bolivia is not significantly elevated above background. This is so even though Bolivian crocidolite has been used for the past 60 years both commercially and residentially in all three cities. Dalenz did indeed say: “Asbestos is exploited from one zone in the county . . . At present, there is no indication of a relationship with lung cancer and mesothelioma” (in Bolivia). This is consistent with Shedd’s earlier impressions that mesotheliomas were not reported in the Bolivian crocidolite mining areas.

The most likely explanation for the failure to find a significant elevation of mesotheliomas in these three Bolivian cities, despite the large populations at risk from the long and extensive residential and commercial use of crocidolite containing products as mentioned above and described in more detail below, is related to an increased fiber width distribution and a concomitant reduction in the ‘Stanton fiber size’ fraction. Similar findings also probably explain the paucity of mesotheliomas in the Finnish anthophyllite, South African amosite, and African Transvaal crocidolite workforces, findings which have been reviewed by others. These findings are also consistent with the conclusions reached by Wylie et al. on the role of fiber width and carcinogenicity.
he did in La Paz and Cochabamba with is too young to have contracted mesothelioma from the work mesothelioma with some work histories, the 32-year-old man mesothelioma cases reported herein. Of two cases of pleural these populations were exposed within the period of latency (one million people per year on average) and the length of time over which (240 years). Nonetheless, the number of cases found in this investiga-
onfamilial history so he conceivably may have incurred exposure to African crocidolite. Virtually no occupational histories were available for the mesothelioma cases reported herein. Of two cases of pleural mesothelioma with some work histories, the 32-year-old man mesothelioma cases reported herein. Of two cases of pleural these populations were exposed within the period of latency (one million people per year on average) and the length of time over which (240 years). Nonetheless, the number of cases found in this investiga-
nonfamilial history so he conceivably may have incurred exposure to African crocidolite. Virtually no occupational histories were available for the mesothelioma cases reported herein. Of two cases of pleural mesothelioma with some work histories, the 32-year-old man mesothelioma cases reported herein. Of two cases of pleural these populations were exposed within the period of latency (one million people per year on average) and the length of time over which (240 years). Nonetheless, the number of cases found in this investiga-
nonfamilial history so he conceivably may have incurred exposure to African crocidolite.}

| Table 4. Cases Reported as ‘Mesothelioma’ or ‘?Mesothelioma’ in Santa Cruz |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Case No. (Bx #) | Age /Sex | Site | IHC | Comments (Institution) |
| 1 (1580-00) | 54/M | Pleura | – | Histology compatible with Malignant epithelial mesothelioma (ONCOS) |
| 2 (4860-02) | 66/F | Left lung | – | Benign fibrous mesothelioma (CPS) |
| 3 (3528-09) | 45/F | ‘Epiplon’ | PanCK + + EMA + + CEA – | Malignant epithelial Mesothelioma (ONCOS) |
| 4 (1113-06) | 59/F | Lung | EMA + CEA – TTF1- HMB45 - (ONCOS) | Lung tissue infiltrated by giant cell, undifferentiated tumor; IHC supports dx of malignant epithelial mesothelioma |
| 5 (3544-06) | 44/F | Omental | – | Cystic papillary tumor with microcalcifications; ‘histology is compatible with well differentiated papillary mesothelioma’ (ONCOS) |
| 6 (2997-07) | 40/M | Inguinal mass | – | “Fragments of fibroadipose tissue infiltrated by a predominantly solid, well differentiated tubular malignant tumor; Adenocarcinoma and malignant mesothelioma are considered in the differential diagnosis” (ONCOS) |
| 7 (4694-07) | 52/M | “Epiplon mayor” | – | “Histological findings compatible with malignant epithelial mesothelioma” (ONCOS) |
| 8 (0853-08) | 46/F | “Lung & pleura” | – | “Malignant round cell tumor with nodular infiltration of the visceral and parietal pleura compatible with malignant epithelial mesothelioma” (ONCOS) |
| 9 (1042-08) | 70/M | Right parietal pleura | – | “Connective tissue fragments and lung infiltrated by malignant giant cell undifferentiated solid tumor. The histological features found indicate the primary differential is between mesothelioma and carcinoma.” (ONCOS) |
| 10 (3335-08) | 31/F | ‘Lung & Pleura’ | VIM + Calret + EMA + Leu-100- | “Histologically & IHC compatible with malignant Mesothelioma” (ONCOS) |
| 11 (3620-08) | 58/F | ‘Lung’ | – | ‘Undifferentiated malignant tumor with giant cell infiltration in adipose, connective, and muscular tissue. The histological appearance suggests primary origin to be mesothelial’ |
| 12 (137-09) | 57/F | ‘Mesoappendix’ | – | ‘Fragments of fibroadipose tissue infiltrated by malignant glandular tumor. The histological appearance is more likely to be carcinoid, tubular adenocarcinoma mesothelioma’ (ONCOS) |
| 13 (4694-07) | 42/F | ‘Pulmonary metastases, primary unknown’ | EMA + CEA- CK20- AE3/5 + TTF1- Pr6- Calret+ | ‘Histologically and IHC compatible with malignant epithelial mesothelioma’ |

Ascertainment and Exposure Considerations

Some cases of mesothelioma may have been missed due to a failure to reach hospital or shortened natural lifespan. We cannot tell precisely the extent to which these were confounding. However, access to medical care, reliance on traditional medicine and shortened lifespan are related to ethnicity and socio-economic status (SES). Indeed, the lifespan of the poorer segments of society is ca 45 years old22-24 and since mesothelioma generally occurs after the age of 50, many in the lower SES groups would have died from competing causes before developing mesothelioma. However, the lifespan of the upper SES groups exceeds 70 years which would be adequate to ascertain cases if they were occurring.

Confounding would therefore be more likely if indigenous groups were preferentially affected for these factors and there was no exposure to the segments of the population in the higher socio-economic groups. However, that was not the case. Indeed, many homes in La Paz (eg, in the upscale
neighborhood of Achuamani) have blue asbestos shingles. (Fibrolit, personal communication, 2011). Therefore, significant numbers of people in upper SES groups in La Paz and other cities in Bolivia have been exposed to Bolivian crocidolite but mesothelioma clusters have not been recognized amongst them. This strongly suggests access to medical care was not a limiting factor since they could avail themselves of hospital facilities. The distribution of crocidolite containing products through various social strata is also well illustrated by the extensive commercial use of crocidolite containing roof tiles and shingles in the major Cochabamba medical center for more than 40 years (Figures 2a & 2b [hospital roof]) and on the roof of the old Calatayud market. (Fibrolit, personal communication, 2010). Moreover, the size of the populations of the three cites at risk in the upper SES strata were quite sizable over the relevant period of risk, from 1950 to 1990 with a latency of 20 years (see Table 1 and the periods at risk were very long and well within latency for the development of mesothelioma.

Dalenz said “one has to admit that there are cancer cases, particularly in the marginal urban areas, whose population does not have access to medical centers and whose contribution to a sub-registry is difficult to quantify.” Still, in other parts of the world with relatively little access to medical centers (eg., central Mexico, New Caledonia or Turkey) historical exposures to dangerous fiber types have occurred for decades and produced clusters of mesotheliomas that were eventually recognized and reported. One would have expected after six decades of continued use of Bolivian crocidolite the same would apply to the so called ‘marginal’ areas of Bolivia and clusters of mesothelioma attributable to the long term use of Bolivian crocidolite would have been found.

A brief summary of the domestic and international distribution and use of these crocidolite containing products is given below as it underscores the extensive distribution of these materials amongst the major populations in Bolivia and to certain specific locations outside the country. It thus emphasizes the extent to which some segments of the Bolivian population have been exposed. Despite these exposure pathways and parameters, no mesothelioma clusters have been identified in relation to the presence of any of these materials.

Domestic Distribution of Bolivian Crocidolite - Containing Products and Exposure Pathways

Cochabamba

The major crocidolite containing products were roof tiles, shingles and water tanks produced primarily by the new Fibrolit plant described below. Historically, at least three crocidolite plants (Ottocar, Banco Minero, and the Old Fibrolit plant) operated near the town center and all were within 2 km of the main hospital complex of the San Simon Medical College. (Figures 3 & 4). At least two more (UNIDO, new Fibrolit) were found just outside the city (Figures 3 & 4) whilst two others (COMACO, YPFB) were in or near the city and used the Bolivian crocidolite in their production lines (see below). These facilities were a source of environmental and residential fiber exposure since, historically fiber spilled downtown during transport to and from the plants.

‘Banco Minera’ plant

There was one ‘Banco Minero’ in each town. These served as ‘mining’ banks (Fibrolit, personal communication, 2011). In Cochabamba, the Banco Minero was located near the slaughterhouse in a populated area slightly outside the city centre ca 2 km from the main square (Figure 3A) (Tejada, personal communication, 2011). The Banco Minero was started in the 1940’s after the Chaco war. It classified fiber for export (Ramirez, personal communication, 2009). After
the other plants were established in ca 1950, the Banco Minero took asbestos from many mines and producers. (Fibrolit, personal communication, 2011). Bags of the mineral were always unloaded manually (Fibrolit, personal communication, 2011).

‘Old Fibrolit’ plant

The first Fibrolit plant was originally one block from main square (Figure 3B). Bags of crocidolite would be delivered there before they went to the Banco Minero for milling and bagging ca. 2 km away (Fibrolit, personal communication, 2011). The Fibrolit eventually bought the Banco Minero plant to supply their own plant and others as well (eg., YPFB oil refineries).

Old Fibrolit processing plant

This plant was originally on Ave America from 1950 to 1982 (Figure 3C). It then moved to km 3 on the Cochabamba to Santa Cruz road also known as Route 4 (Figure 3D). Van Orden and others (2011, personal communication) have given some description of this plant in its present yet ‘historical’ operational state but this has yet to be published. An earlier partial account by Bliss and Ankers is briefly presented here.12 Their study of the Bolivian crocidolite industry was done on behalf of UNIDO in the late 1980s and is described in Appendix 1. The milling and the fibro-cement plant are presently located adjacent to each other. Both are very elemental. It was been noted that dusty conditions prevailed in each facility.
Although located at least 3 km from the center of Cochabamba, there are various suburban homes and work places nearby which may be subject to environmental residential exposure (Figure 4).

Otacar family plant and factory

The Ottocar family was the biggest buyer of blue asbestos in Cochabamba for many years. It began in 1946 and originally owned both a classifying plant and a production factory for Bolivian crocidolite. (Ramirez, personal communication, 16 April 2009)

Otacar classifying plant

The classifying plant was located in the center of Cochabamba at the corner of Calle Columbia and Miralla Tamulse (Figure 3E). (Ramirez, personal communication, 2009) There was much dust in the air. The building only had a roof and four walls. There was no ventilation. The work continued for 8 h a day. Workers unloaded the crocidolite into jute bags which they put in a small open storage room. It was then taken out of the bags and carried in wheel barrows to be put into the classifier. Most of the fiber was loose. It is not clear where the waste was dumped though some of it may have been purchased by YPFB to make pipe insulation (Gallo & Ramirez, personal communication, 2009). The classified crocidolite was purchased by various companies including YPFB (initially Petrobras), Ottocar, La Belgica owner of the Montero sugar mills in Santa Cruz, and also for Fibrolit.

Otacar production plant

The production plant (Figure 3E) made shingles and tanks from 1950 to 1975.29

UNIDO plant (PLANTA DE ONUDI)

The UNIDO plant had been an experimental processing plant of blue asbestos built by the joint cooperation of UNDP, UNIDO and the Bolivian government, under project DP/BOL/68/520 that began in 1968 in Cochabamba at 9 km on the road to Santa Cruz. The UNIDO plant bought asbestos from Banco Minera. Its former Director, Sr Jimenez Gallo, said that he worked there with blue asbestos from 1973 to 1977 (Gallo, personal communication, 2009). Thirty men were employed at any one time, over the years, amounting to ca 200 in total. While dust measurements were done at the plant there were no data left. Bliss and Ankers12 said that no data left. Similarly, there were no personnel records and probably no employee lists left. Bliss and Ankers12 said that grade “#6 is the remainder/lefterover (residue material used for insulation).” YPFB, the national oil company, initially bought crocidolite from Banco Minera. The company used crocidolite to insulate their pipes and tanks and had a department to make pipes exclusively for them. Short fiber was used in the pipes since 1946 (Ramirez, personal communication, 2009) The exact location of the plant in Cochabamba could not be determined. Ramirez said crocidolite may also have been used as drilling mud.

Textiles

Long crocidolite fiber was used for spun thread textiles.29

Filters

Medium length fiber was used in various filter media (also see below under “United States”) by the chemical industry for the purification of different harsh chemicals and gases (“thermic air freshener”).

Brakes and brake lining

Medium length crocidolite fiber was used in the automotive industry for brakes and brake linings.29

Paper and cardboard foil

Medium length crocidolite fiber was used in the production of thermic coating in fine cardboard foil.

Floor tiles

“Polyvinyl crocidolite asbestos foil” was used in some floor tiles.29

Plastic reinforcement, construction and ceiling tiles

Crocidolite was also used in construction, plastic reinforcement, and ceiling tile production (Ramirez, personal communication, 16 April 2009)

Duralit Chrysotile plant

This plant is located 7 km outside Cochabamba (Figure 3G). The plant apparently used some Bolivian and Cape South African crocidolite for testing purposes early in its history.

COMACO plant

COMACO is a major producer of concrete cement products. Historically, it purchased Bolivian crocidolite for some of its product lines (Fibrolit, personal communication, 2011) and one of its plants was located in the city of Cochabamba (Figure 3H). Today, it is based in Santa Cruz.

The major product lines using the Bolivian crocidolite made shingles, tiles and water tanks. However, other products were produced in Cochabamba and distributed through the city and to other parts of Bolivia.

Pipe insulation, general lagging, drilling mud

Medium length fiber was sold to oil refineries, sugar refineries, and other companies for pipes and general lagging on, for example, furnace coating and towers in the petroleum refining industry.29 Bliss and Ankers12 said that grade “#6 is the remainder/lefterover (residue material used for insulation).” YPFB, the national oil company, initially bought crocidolite from Banco Minera. The company used crocidolite to insulate their pipes and tanks and had a department to make pipes exclusively for them. Short fiber was used in the pipes since 1946 (Ramirez, personal communication, 2009) The exact location of the plant in Cochabamba could not be determined. Ramirez said crocidolite may also have been used as drilling mud.
Precious metals/artisan work

Bolivian crocidolite was used in “gold or silver work to produce artistic objects in pressed or molded masses”\(^2\). It was also used in sculptures (Fibrolit, personal communication, 2011).

Distribution to Bolivian Towns Outside of Cochabamba

Sixty percent of all of the Fibrolit crocidolite products have gone to Santa Cruz (Fibrolit, personal communication, 2011). In addition to shingles, tiles and water tanks, long fiber is used preferentially to line the boilers of the sugar mills commonly found around Santa Cruz.

There were at least 40 distributors in Bolivia of crocidolite containing products. These distributed the products from the factory to the marketplace by private trucks within and outside Bolivia. Fibrolit had a major distribution agency in La Paz. This also made small amounts of crocidolite containing products.

Other, Smaller Deposits of Bolivian Crocidolite

Taritja

Taritja (1905 m) is a city of 132 000 located in the south of Bolivia ca 96 km north of the Argentine border. Founded in 1574, it was formerly established as part of Bolivia in 1825. It is recognized for its beautiful colonial architecture and vineyards.

The crocidolite deposits and mines near Taritja are very small and consist largely of short fiber (Fibrolit, personal communication, 2011). This made their exploitation economically unfeasible (Ramirez, personal communication, 2009).

Eastern Bolivia near the Mutun iron deposit

The iron deposit near Mutun in the extreme eastern part of Bolivia along the Brazilian border around 30 km south of Puerto Suarez (Figure 1) is one of the largest in the world. There is a small amount of Bolivian crocidolite near the Mutun iron mining area\(^3\). The area is rather sparsely populated but conceivably workers, their families, certain towns’ folk, and others living along the distribution lines of the ore may incur exposure to crocidolite fiber.

International Distribution

Chile

Bolivian crocidolite was sold to Chile through Arica and Antofagasta and transported by train either through La Paz or Potosi (Ramirez, personal communication, 2009). Sales were made from 1950 to 1980. It was sold to Chile for the production of fibrocement water pipes and tubes. The use of asbestos cement pipes in the North of Chile was documented by Schull (unpublished) in Putre, San Miguel, Chungara, Arica and Chanaral as part of their Multi-Andean Genetic Health Programme\(^4\).

Bolivian crocidolite was also exported to the United States through Chile. This was discontinued in 1972. The location of the Chilean plants that processed the Bolivian crocidolite is not known. However, review of the historical records of the regions in the north of Chile for diverse cancer types failed to reveal a mesothelioma excess.

Argentina

Argentina used long fiber Bolivian crocidolite to make firefighter’s clothes sold under the name ‘Christ Desu’ (Ramirez, personal communication, 2009). The location of the Argentine plants that processed the Bolivian crocidolite was in a suburb of Buenos Aires. However, we are not aware of reports of mesothelioma clusters in this part of Argentina where these materials would have been processed. No doubt, given the highly fibrous nature of the material, this would have been a very dusty operation (Figure 5).

Brazil

Petrobras initially used Bolivian crocidolite in Brazil (Ramirez, personal communication, 2009).

United States

Bolivian crocidolite was stockpiled for strategic use in the production of filters\(^5\) (see Appendix 2). Gaensler and Goff\(^6\) reported the use of Bolivian crocidolite, in combination with South African, in their study of asbestos related disease in filter paper plant workers in the Boston area. Knudson\(^7\) recommended the use of Bolivian crocidolite in cigarette filter papers. Some may also have been used for a short time in school notebook paper as well.

Storage and Transport of the raw asbestos

The crocidolite was carried in paper and jute bags. Some were re-used for other purposes. The risk of developing mesothelioma from the handling of raw asbestos contaminated jute bags is well known.\(^8\) Breakage of bags and spillage of crocidolite also took place en route from the mines in the Chapare ca 220 km from Cochabamba. Historically the road was very bad which caused more bags to break particularly since the asbestos was initially transported by mule trains of 100 to 150 animals. Afterwards it was brought by truck (Fibrolit, personal communication, 2011). The mineral in transport was 85% pure\(^9\).

Figure 5. Hand specimen of long fibre Bolivian crocidolite used for textiles and boiler insulation.
Other Sources of Potential Ascertainment Bias

It could be argued that the individuals at greatest risk outside of the plants were those who installed the tiles, shingles and water tanks from sawing or drilling these materials. It could also be argued that such individuals were largely from the lower classes. However, some residents would also have installed these materials themselves as the instructions for doing so were simple and straightforward.

Clearly, if the attendant risk was so high, clusters of mesothelioma would have been found in these workers after six decades. It could be argued that since such work was done outside the exposures were just too low but that if that was the case it would support the notion of a mesothelioma threshold.

MISDIAGNOSIS

The periods of ascertainment for the three cities (La Paz: 1978/1982; 1988–1992; Santa Cruz: 1998–2008; and Cochabamba: 2003–2009) were contemporaneous with the development and existence of the diagnostic tools presently used to diagnose mesothelioma. Thus, by 1978 which is the starting date for the case ascertainment done in the present study, the histological, histochemical and immuno-histological tools for the recognition of mesothelioma on small tissue samples had been established in conjunction with necessary radiological diagnostic methods (see Appendix 3). Moreover, the major hospitals in the three largest cities of Bolivia that were the subject of this study were equipped with the radiological and pathological tools needed to diagnose mesothelioma by 1978. The cases were also reviewed by experienced senior pathologists and radiologists.

Seven of the 13 Santa Cruz cases (Table 4) should probably be excluded. Cases 9 and 11 had predominant histological features uncommonly found in mesothelioma that make the diagnosis suspect (giant cell features). Case 2 (‘benign fibrous mesothelioma of the pleura’), case 5 (well-differentiated papillary mesothelioma of the peritoneum), and case 6 (tunica vaginalis mesothelioma) are histological variants not causally associated with asbestos exposure. Case 12 is also suspect as it is merely listed as ‘primary site undefined’. Case 13 simply refers to tumor as ‘primary site undefined’ for 82 men (rate 8.5) and 60 women (rate 6.0) for neoplasms classified from 1978 to 1982 out of a total of 2734 (839 men; 1795 women). Similarly, tumors were also categorized as ‘Primary site undefined’ for 63 men (100.1 rate) and 130 women (160.5 rate) for neoplasms classified from 1988 to 1992 out of a total of 4,597 (1,505 men; 3,092 women). There is no way to be certain some mesotheliomas were not placed in these categories.

Tuberculosis

Historically, pleural tuberculosis (TB) has been the major source of historical diagnostic confounding for mesothelioma. Indeed, the cases of mesothelioma discovered by Wagner et al. in the Cape crocidolite mine fields were found in miners thought to have resistant pleural TB. Some of the pathologists that participated in the present study said cases of thickened pleura were frequently biopsied. However, Bolivia has one of the highest rates of TB in the Western hemisphere. As TB is not widely screened in Bolivia, pleural TB could be a source of confounding.

Nosological classification

The categorization of mesotheliomas by the nosologists did not appear to be problematic. This was done using the standard ICD system (CEI in Spanish) (also see above). There were tumors, nonetheless, classified as ‘primary site undefined’ for 82 men (rate 8.5) and 60 women (rate 6.0) for neoplasms classified from 1978 to 1982 out of a total of 2734 (839 men; 1795 women). Similarly, tumors were also categorized as ‘Primary site undefined’ for 63 men (100.1 rate) and 130 women (160.5 rate) for neoplasms classified from 1988 to 1992 out of a total of 4,597 (1,505 men; 3,092 women). There is no way to be certain some mesotheliomas were not placed in these categories.

MESOTHELIOMA THRESHOLD, FIBER WIDTH, AND MECHANISTIC CONSIDERATIONS

The apparent failure to see a mesothelioma excess due to Bolivian crocidolite suggests the exposures incurred by the residents in the three major cities of Bolivia contained too few Stanton fibers to reach a mesothelioma threshold. Failure to produce mesotheliomas in animals using Bolivian crocidolite, albeit in only a few studies, is also supportive evidence for a mesothelioma threshold.

Mechanistically, it is still not clear what this means on a cellular level. For example, since the mechanism underlying asbestos related diseases centers upon the macrophage, the diameter of the macrophage is directly related to its ability to clear the fiber. However, some fibers in a certain width range (e.g. 0.6 - 1.0 μm) can apparently reach the deep lung and translocate to the pleura as do fibers much thinner than those (0.25 μm).

However, epidemiological and experimental data suggest that fibers in the wider range (vs) are less potent than the thinner ones for the induction of mesothelioma (<0.25 μm). Assuming fibers of a similar length greater than 5 μm long, it is not clear if an ‘intra-cellular’ threshold exists for thick versus thin fibers even if they occupy the same intracellular volume. Simple experiments could be designed to investigate this possibility.

Implications for Other Fiber Types

These findings also support the more general proposition that ‘wide’ fibers found as amphibole cleavage fragments and
so called elongated particles of any type are clearly less toxic than presently alleged 47,48 and are therefore not able to produce mesothelioma at all 49. These materials are ubiquitously, commonly found for example in quarried aggregate stone used for myriad purposes throughout the world. Logic thus dictates these materials would produce large numbers of mesothelioma clusters if they were as potent as true amphibole asbestos fibers. However, to our knowledge, none has been seen commonly found for example in quarried aggregate stone used for myriad purposes throughout the world. Logic dictates these materials would produce large numbers of mesothelioma clusters if they were as potent as true amphibole asbestos fibers. However, to our knowledge, none has been seen.

Acknowledgements: The authors would like to thank Fibrolit, Dr. Ricardo Ramirez, co-author of this paper and mining engineer who has studied the mine for many years and Sr Jimenez Gallo who was the former Director of the UNIDO plant for their background information to this study.

Disclosure: Some $7,000 of financial support came from RJ Lee which represented about 5% of the total cost of the study; other finance came from personal funds. RJ Lee had no role in the design of the study, data collection, analysis or interpretation of results.

REFERENCES

APPENDIX 1

The Milling Plant: “The mill operates all year round and employs four people. The roofed mill building is open on both sides. Asbestos that arrives from the mine is piled up near the rolling mill and it is fed by manual shoveling. The plant has a preliminary grinding place and material that cannot be ground is separated and piled aside. The milled product is manually separated and transported in wheelbarrows to a hammering mill, where it is again introduced to the mill using shovels. … From this recollection, the material is transported manually towards one of the two sieving machines. … The total production reaches on average between 2–3 metric tons per day. Four people operate the plant, working for eight hours a day, five days a week.”

APPENDIX 2

“Bolivian crocidolite was stockpiled for strategic use in the production of filters. (Blue asbestos) shall conformed with National Stockpile Specification P-80-R, dated April 17, 1952, which designates that the material purchased shall be Bolivian crocidolite asbestos or its equivalent. Three grades are covered, as follows: Crude No. 1, a minimum of 85% (by weight) of which shall be in fibers three-fourths of an inch in length or longer; Crude No. 2, a minimum of 85% of which shall consist of fibers three-eighths of an inch to three-fourths of an inch in length; and Run-of-Mine (crude or milled), a minimum of 90% of lumps and fibers of which shall be retained on a No. 16 sieve. The material shall contain not more than 2% of moisture and not more than 5% of foreign matter. The specification includes items covering methods of test, etc. Details of sampling and inspection are omitted as this material is no longer being purchased for the stockpile.”

APPENDIX 3

Thus, by 1978 which is the starting date for the case ascertainment done in the present study, the histological, histochemical and immunohistological tools for the recognition of mesothelioma on small tissue samples had been established in conjunction with necessary radiological diagnostic methods. Indeed, historically, diagnoses of mesothelioma were not generally made before 1960 though reports certainly documented the existence of rare examples of these tumors. This is well exemplified by the discussions of the principal author with Sir Richard Doll in 2003 in Oxford. Thus: “Chris Wagner had recently died and his wife and colleague, Dr. Margaret Wagner, were my dinner guests in Oxford. Margaret recounted the difficulties Chris had in convincing his colleagues in South Africa in 1958 that the tumors he recognized in the crocidolite miners were mesothelioma (as described by Wagner in Henderson) 39. Sir Richard Doll said he felt there was at least one mesothelioma amongst the ‘lung tumors’ he found in the Rochdale textile asbestos factory workers but pathologists were very reluctant to make the diagnosis. Sir Richard said this was because Rupert Willis, the pre-eminent tumor pathologist at the time held great sway and had taken the view, I believe quite correctly, that such tumors were exceedingly rare and could only be diagnosed with full autopsy. Willis confirmed this to me in person in 1977 when I visited him at his home in the Wirral in the north of England. Things changed after Wagner’s 1960 publication 40 on the finding of mesotheliomas in the South African mines and thereafter Chris developed some of the first histochemical stains to further refine the accuracy of the diagnosis. By 1978 additional histochemical and immuno-histochemical stains had been developed and these constituted a basic staining panel for confirming the diagnosis on tissue biopsies.”

** Available on request from the authors.

Appendices