

## Risk of Mesothelioma Among Women Living Near Chrysotile Mines Versus US EPA Asbestos Risk Model: Preliminary Findings

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**Introduction.** The risk of asbestos diseases cannot be measured directly in populations with low level chrysotile asbestos exposure. Risk assessments must be used to extrapolate risks from past heavy industrial asbestos exposures to today's low chrysotile exposures. We tested the US Environmental Protection Agency (EPA) mesothelioma risk model in a population having experienced relatively high and mostly non-occupational chrysotile exposures.

**Methods.** Female mesotheliomas first diagnosed from 1970 to 1989 in chrysotile asbestos mining districts (Asbestos and Thetford) were identified from the Quebec Tumour Registry and hospital records gathered throughout the province. Diagnoses were reviewed by three pathologists. An international expert panel estimated historical ambient exposure levels in these districts. A 'time-area-job-family exposure' matrix was derived from these estimates, occupational and cohabitation exposure estimates and a survey of 817 female residents. We applied the EPA mesothelioma incidence model to the population time-area-job-family exposure matrix and compared this predicted incidence with that actually observed.

**Results.** Ambient airborne asbestos exposures were between 0.1 and 3 fibres/ml before 1970. The EPA asbestos risk model predicted 150 (range 30-750) female mesotheliomas in Asbestos, while only one case (peritoneal) was observed; 500 cases (range 100-2500) were predicted in Thetford Mines, while 10 cases (pleural) were observed. These large discrepancies cannot be explained by random or systematic errors.

**Keywords:** amphibole; asbestos; chrysotile; cohabitation; linear carcinogenesis model; mesothelioma; neighbourhood; occupational exposure; risk assessment; tremolite

### INTRODUCTION AND BACKGROUND

Cancer risk today at 'low' chrysotile asbestos exposures (<1 fibre/ml in workplaces, <0.0005 fibres/ml in non-occupational settings) cannot be observed by epidemiological or toxicological methods. Low risks must be estimated using quantitative risk assessments (QRAs) that extrapolate risks in past occupational cohorts (30-300 fibres/ml) to exposures today. Since 1980, regulatory authorities have conducted such QRAs to estimate cancer risks related to low asbestos

exposures, targeting mixtures of chrysotile and amphiboles (Nicholson, 1986; HEI-AR, 1991).

Regarding mesothelioma, up to four occupational studies have been used for exposure-risk analysis. Unfortunately, 'there are serious weaknesses in all four studies, particularly for assessing the effects of chrysotile' (HEI-AR, 1991, chapter 6, p. 15), due to ill-defined concentrations of chrysotile and amphibole mixtures. Moreover, the multistage model for exposure-risk modelling was fitted fully to only one cohort (Peto *et al.*, 1982). The uncertainty of the model is thus large, yet usually discounted.

A small region of Canada's Province of Quebec produced most of the world's asbestos until 1954 and remained the world's largest asbestos exporter until

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recently. Between 1891 and 1980 asbestos fibre emissions and fallout were visible; residents experienced exposures intermediate between those of past asbestos workers and those of today's urban populations. We undertook a research programme to quantify risks and specify risk factors for asbestos-related diseases in women residing in that chrysotile mining area (Siemiatycki, 1983; Camus and Siemiatycki, 1998; Camus *et al.*, 1998; Case *et al.*, 2002). We here present preliminary findings of our validation study of the US Environmental Protection Agency (EPA) mesothelioma model.

## MATERIALS AND METHODS

### Case ascertainment

We visited hospitals throughout the populated portion of Quebec province. We identified, from hospital records, oncology archives and pathology records, all women aged 30 years or more for which a possible mesothelioma was mentioned in their chart between 1970 and 1989. Diagnosis was reviewed by two pathologists for subjects for whom we could obtain pathological tissue blocks or slides. We accepted all cases classified as 'definite', 'probable' or 'possible' mesothelioma by either of the two pathologists or, if pathology material was unavailable, by an algorithm based on a 10 point clinical rating score by a third pathologist (B.W.C.) (Case *et al.*, 2002). Through hospital records and interviews of relatives we identified all possible mesotheliomas (pleural or peritoneal) in females residing in Quebec's chrysotile mining districts (Asbestos and Thetford) at the time of diagnosis. These made up the observed cases.

### Risk assessment model and predictions

The US EPA (Nicholson, 1986) used the asbestos-mesothelioma risk model developed by Berry (Newhouse and Berry, 1976) and Peto (Peto *et al.*, 1982):

$$I_M(t) = \lambda_M(t) \\ = K_M \times c \times [(t - t_{\text{start}} - 10)^3 - (t - t_{\text{end}} - 10)^3]$$

where  $\lambda_M(t)$  is the standardized mesothelioma incidence rate,  $K_M$  is the gradient of  $\lambda_M(t)$  per fibre/ml, holding the time parameters constant, and  $c$  is the asbestos fibre concentration [(fibre > 5  $\mu\text{m}$ )/ml] between  $t_{\text{start}}$  and  $t_{\text{end}}$ . The model does not distinguish between pleural and peritoneal mesotheliomas despite their different aetiologies. The EPA estimated the linear exposure-risk gradient to be  $K_M = 10^{-8}$ . We applied this model to the exposure histories of the study population. We estimated asbestos exposure levels for each year of a person's lifetime and estimated the risk for each person surveyed. This risk

was then applied to the whole study population of the same birth cohort stratified by 5 yr periods and by mining district over the 1970-1989 period, itself stratified by 5 yr periods.

### Historical exposure assessment

Asbestos exposure levels in 'fibre/ml' were estimated for each year and mining town, according to the methods described previously (Camus *et al.*, 1998), and for each of three possible exposure circumstances: (i) neighbourhood exposure resulting from asbestos mining/milling emissions; (ii) 'cohabitation' exposure resulting from dust brought home by asbestos workers; (iii) occupational exposure.

The only 'hard data' on airborne asbestos levels in the asbestos towns were continuous dust measurements carried out since 1972, 1 day fiber measurements carried out annually by industrial hygienists since 1974 and two recent exposure surveys (Gibbs *et al.*, 1980; Sébastien *et al.*, 1986). For earlier periods we assessed the following indirect evidence.

1. Annual production volumes by mining town from 1900 to 1984.
2. Historical information of the industrial and mining processes.
3. Extrapolations back to 1900 of the relation between airborne levels, annual production and controls in 1972-1984.
4. Past visible asbestos depositions estimated from a survey of 817 elderly female residents.
5. Aerosol dispersion modelling to estimate airborne asbestos levels in the town of Asbestos before the onset of dust controls.
6. Application of the relation between lung burden and occupational exposure histories of Quebec miners and millers (Sébastien *et al.*, 1989) to the lung burdens of 22 residents without occupational exposures (Case and Sébastien, 1989) to estimate their past exposures.
7. Review of these data by a panel of five experts to estimate past 'neighbourhood exposures' in the three main mining towns for each calendar year since 1900. Average annual ambient levels would have peaked at ~1 fibre/ml between 1940 and 1954. The panel thought that true concentrations must have been less than three times smaller or greater than their best estimates.

Seventy per cent of the women had lived with an asbestos worker. We derived 'cohabitation exposure' estimates from a set of 10 autopsies of residents who lived with asbestos workers. We estimated cohabitation exposures to be 0.1-1.5 fibres/ml above neighbourhood levels. External sources corroborated these estimates.

Our 1989 survey showed that ~5% of local women had worked in the industry or had mended bags used

for shipping asbestos. We estimated such past 'occupational exposures' to be ~3–15 fibres/ml.

Finally, in 1989 we surveyed a representative stratified sample of 817 elderly female residents in the study agglomerations about their lifetime residential, occupational and cohabitation exposure histories. Combining these histories with estimated past exposure levels, we estimated a historical town-year-exposure matrix to which we applied the EPA asbestos-mesothelioma model.

### RESULTS

The average cumulative exposure of the study population from all sources was 25 fibres/ml yr (168 h/week) or a 'worker-equivalent exposure' of 105 fibres/ml yr [plausible interval (PI) 21–525 fibres/ml yr]. Over the 1970–1989 study period the study base totaled 221 375 person yr, for which the EPA model predicted 150 (PI 30–750) mesotheliomas in females in Asbestos and 500 (PI 100–2500) in females in Thetford Mines.

In comparison, a single mesothelioma (peritoneal) occurred in the Asbestos district. Ten mesotheliomas (all pleural) were observed in females in the Thetford Mines district. More detailed exposure information is given in Case *et al.* (2002).

The risk of mesothelioma (pleural and peritoneal) was overestimated 150-fold (PI 30–750) in the Asbestos area, 35-fold (PI 7–175) in the Thetford Mines area and 50-fold (PI 10–250) in both areas combined. The mesothelioma incidence rates were 67.5 per million person yr in the Thetford area (95% CI 32.4–124.1 per million person yr) and 13.7 per million person yr in the Asbestos area (95% CI 0.35–76.2 per million person yr). In comparison, mesothelioma incidence among Quebec women was about 4 per million person yr.

### DISCUSSION AND CONCLUSIONS

We observed an excess of mesotheliomas in this population relative to the female population of Quebec. Still, the observed incidence was orders of magnitude smaller than that predicted by the US EPA model. Although risk assessments should be based on conservative or precautionary assumptions, a two order of magnitude overshoot for chrysotile exposures could be an overkill that would hinder risk management if it went unrecognized, particularly when comparing the risks of chrysotile to the risks of substitute fibres (Camus, 2001).

There are several possible reasons for the discrepancy between the EPA and our observations and between the risk in Asbestos and Thetford Mines (Camus, 1997; Siemiatycki and Boffetta, 1998). Amphibole fibres are more carcinogenic than chrysotile fibres for mesothelioma. The cohorts on which

the EPA based its estimates were exposed to substantial levels of amphiboles, thereby tending to overestimate risks in chrysotile-exposed populations. Likewise, the risk could be greater in Thetford Mines than in Asbestos due to the greater tremolite content in some of Thetford's mines (McDonald and McDonald, 1997). Another possible explanation is that the model itself may be wrong in form or in its parameter estimates. Finally, the exposure-effect relationship may be non-linear.

**Acknowledgements**—The authors especially thank Drs Andrew Churg and Victor Roggli, who provided pathological reviews, Drs Graham Gibbs, Morton Corn and Patrick Sébastien and the late Dr William Nicholson who (with B.W.C.) formed the expert exposure panel, Louise Nadon, who assisted in data analysis, and Ms Marie Beauchemin, who conducted the interviews of proxies for mesothelioma cases in Thetford Mines, Québec. This work was supported by a series of grants from Health Canada to Dr Siemiatycki, from NHRDP Canada to Drs Siemiatycki, Case and Patrick Sébastien and by a grant from the Canadian Institutes of Health Research (CIHR) to Drs Case and Siemiatycki.

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