Cherrie, J. W., McElvenny, D. and Blyth, K. G. (2018) Estimating past inhalation exposure to asbestos: a tool for risk attribution and disease screening. *International Journal of Hygiene and Environmental Health*, 221(1), pp. 27-32. (doi:10.1016/j.ijheh.2017.09.013)

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Accepted Manuscript

Title: Estimating past inhalation exposure to asbestos: a tool for risk attribution and disease screening

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PII: S1438-4639(17)30431-5
DOI: https://doi.org/10.1016/j.ijheh.2017.09.013
Reference: IJHEH 13133

To appear in:

Received date: 6-7-2017
Revised date: 26-9-2017
Accepted date: 29-9-2017

Please cite this article as: Cherrie, John W, McElvenny, Damien, Blyth, Kevin G, Estimating past inhalation exposure to asbestos: a tool for risk attribution and disease screening.International Journal of Hygiene and Environmental Health https://doi.org/10.1016/j.ijheh.2017.09.013

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Estimating past inhalation exposure to asbestos: a tool for risk attribution and disease screening

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Word count: 4399
Abstract: 234 words

Running header: **Estimating past inhalation exposure to asbestos**

Highlights

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- There is no good way to identify at risk individuals for screening for mesothelioma.
- Mesothelioma screening could maximise access to trials of novel therapies.
- Asbestos exposure can be assessed from information obtained from the worker.
- Validation show a strong correlation between measured and estimated exposure.
- There is an urgent need to pilot pre-selecting for mesothelioma using this method.

Abstract

Introduction

Late presentation is common in mesothelioma. Reliable assessment of past exposure to asbestos is a necessary first step for risk attribution and for the development of a future screening programme. Such a programme could maximise access to trials of novel therapies and would pave the way for development of novel chemoprophylaxis strategies. This paper describes a method for individual exposure reconstruction along with data from a validation study.

Methods

The exposure assessment method uses only descriptive information about the circumstances of the work that could be obtained from questioning the worker. The assessment is based on the tasks carried out and includes parameters for substance emission potential, activity emission potential, the effectiveness of any local control measures, passive emission, the fractional time the asbestos source is active and the efficiency of any respiratory protection worn.

Results

There was a good association between the estimated and measured exposure levels. Pearson's correlation coefficient between the log-transformed measurements and

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estimates from the model was 0.86, and 95% of the estimated individual values were within about a factor of ten of the associated measured value. The method described would be suitable for pre-selecting individuals at high risk of malignant pleural mesothelioma for screening using appropriate tools and/or enrolment in clinical trials of chemo-prophylaxis.

Discussion

This method is of potential clinical value in developing novel treatment approaches for mesothelioma. Pilot studies to test this approach are urgently needed.

Keywords: mesothelioma, screening, asbestos, exposure

Introduction

Asbestos was widely used in many countries in Europe, North America and elsewhere during the 20th Century. The peak usage in most of these countries occurred in the 1970s (Nishikawa et al., 2008). Most of the asbestos used was chrysotile with a smaller but important proportion of amphibole asbestos. Today many countries have banned the use of asbestos, but in all countries where there was widespread historic use there are still substantial quantities of asbestos that remain *in situ* in both commercial, public and residential buildings. Therefore, the health risks from inadvertent exposure will continue for many decades to come.

The International Agency for Research on Cancer (IARC) has reviewed the evidence for carcinogenicity of asbestos and has concluded that all types of asbestos can cause mesothelioma, lung, laryngeal and ovarian cancer, with more limited evidence for causation of cancers of the colorectum, pharynx and stomach (Straif et al., 2009). For mesothelioma

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and lung cancer, the dominant asbestos-related malignancies, the scientific evidence shows that the risk of disease is related to the lifetime cumulative exposure. In mesothelioma, the risk differs considerably between asbestos types, with the greatest risk associated with prior exposure to amphiboles. For example, using the algorithm developed by Hodgson and Darnton (2000) suggests there is about a 5% lifetime risk of mesothelioma for 5 fibres/ml.years exposure to crocidolite for someone aged 20 years when first exposed, with the corresponding risks for chrysotile exposure being around 0.03%.

There is a long latency for mesothelioma and for those countries that banned asbestos in the 1970s there are indications that the peak incidence rate has either occurred or will soon occur (Tan et al., 2010). For example, in Great Britain the annual number of mesothelioma deaths has risen from around 500 in 1980 to 2549 in 2014. On the basis of mortality trends over time it is projected that the peak number of mesothelioma deaths will be around the current number for the rest of this decade before beginning to decline thereafter (HSE, 2014). Globally, exposure to asbestos continues without regulation in many countries in the developing world, including those with large populations such as India. This predicts large numbers of asbestos-related mesothelioma and lung cancer deaths in these nations, unless novel effective intervention strategies are defined in the near future.

There are currently no curative therapies for mesothelioma and curative treatment is only possible in lung cancer detected at an early stage. The development of new therapies for both diseases is hampered by the frequency of late-stage acute presentation in patients with declining physical function due to their disease. For mesothelioma patients in England and Wales, the median survival time from diagnosis is 9.5 months, with around 12% surviving 3-

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years (Beckett et al., 2015). In recent series, up to 50% of mesothelioma cases were recorded as having presented as an acute emergency to hospital (Tsim et al., 2014; 2015). Efforts to detect mesothelioma at an earlier stage using radiological screening have so far been unsuccessful (Fasola et al., 2007; Roberts et al., 2009). This may have been due to the lack of an effective means of selecting individuals with a sufficiently high risk of the disease to generate enough screen-positive cases and/or the use of insensitive screening tools, such as computed tomography in these studies (Hallifax et al., 2015; Tsim et al., 2017). Mesothelioma screening is not currently recommended because of the currently limited therapeutic options for the disease. However, recent years have seen much increased research in mesothelioma resulting in the development of a range of novel treatment approaches. Many of these, including trials of radical surgery (Pietro Bertoglio and Waller, 2016) and hemi-thoracic radical radiotherapy (Rimner et al., 2016) or combined multi-modality approaches, are only suitable for the fittest patients with the lowest possible volume of disease. Early detection is therefore an essential component in testing these approaches and ultimately improving outcome. With regard to lung cancer, Wolff et al., (2015) suggest that low-dose computed tomography (LDCT) should be evaluated as a screening tool specifically for former asbestos workers or others at risk, primarily smokers. This is based on evidence from the US National Lung Cancer Screening Trial that has shown that LDCT screening can reduce both lung cancer and all-cause mortality amongst current and former smokers (Detterbeck et al., 2013). To ensure sufficient screen-positive cases, for either mesothelioma or asbestos-related lung cancer, an accurate method of quantifying cumulative asbestos exposure, and thereby calculating risk using a suitable model of the relationship between cumulative exposure and risk would be an essential requirement for development of asbestos exposure-focused screening programmes.

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Chemoprophylaxis is an attractive alternative approach to improving survival in patients at high risk of asbestos-related cancer, and does not require development of expensive screening technologies. Broadly speaking, chemoprophylaxis involves use of preventative therapy to modify the biology associated with carcinogenesis and reduce cancer incidence in patients with clearly definable high levels of risk. Use of therapies with minimal or no side-effects is a prerequisite for chemoprophylaxis. Recent authors have strongly encouraged re-evaluation of chemoprophylaxis in mesothelioma (Neri et al., 2012) after positive trials in breast (Cuzick et al., 2007; Fisher et al., 1998), prostate (Thompson et al., 2003) and colorectal cancer (Rothwell et al., 2012; 2010). Major research groups are actively pursuing this, using high-throughput drug screening to identify novel molecules or existing medications that might be repurposed as chemoprophylactics, but identification of the right population will be required if this approach is to work.

In the absence of effective therapies, or a state compensation scheme is many countries, the only means of redress for many with mesothelioma or asbestos-related lung cancer is to seek financial compensation through civil litigation. However, this generally requires the claimant to establish that asbestos exposures within one or more periods of employment was a material cause of their disease, which requires efforts to trace and document past exposure circumstances and to qualitatively or quantitatively characterise the exposure. The Helsinki Criteria for diagnosis and attribution of asbestos disease (Wolff et al., 2015), suggest that for mesothelioma to be attributed to asbestos exposure there should be “a history of significant occupational, domestic or environmental exposure”, although they caution that

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mesothelioma may occur after lower level asbestos exposure. A method of accurately quantifying exposure would be a valuable tool for this purpose.

The aim of this paper is to describe a method of reconstructing past inhalation exposure to asbestos and to validate the methodology by comparing estimated exposure levels with measured values.

Methods

The method of reconstructing asbestos exposure has been previously described (Cherrie et al., 1996) and there are limited validation data for asbestos and other hazardous occupational exposures (Cherrie and Schneider, 1999). The general methodology has been adapted to form the basis of the Advanced REACH Tool (ART) for estimating exposure to chemicals within the scope of the European REACH Regulations (Cherrie et al., 2011; Schinkel et al., 2011; Tielemans et al., 2008b) and for the Dutch control banding tool Stoffenmanager (Tielemans et al., 2008a). However, neither of these tools enables the assessment of asbestos fibre exposure. We briefly summarise the method here using the terminology of Tielemans et al., (2008b).

The method is based on a simple source-receptor model of exposure incorporating a source term that is dependent on three factors: the substance emission potential (E), Activity emission potential (H) and the effectiveness of any local control measures (LC). Substance emission potential reflects the intrinsic property of the material being handled, e.g. the dustiness of the asbestos containing material, that is assumed to be dependent on the type and proportion of asbestos present, and the extent of bonding in the product, e.g. presence

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of a cement matrix. Activity emission potential describes the way the material is handled and primarily relates to the amount of energy imparted to the material to disperse the contaminant. General dilution ventilation (D) in a workroom will also have an impact on the contaminant concentration (Cherrie et al., 2011).

Three further parameters are incorporated into the basic model: the passive or fugitive emission (Su), the fractional time the source is active (ta) and the efficiency of any respiratory protection (RPE). All these model parameters are assumed to be independent of each other and they are combined in a multiplicative form to estimate the exposure level. The main exception to this is the passive emission term, which is included as an additive factor unrelated to the active source.

For a single source close to a worker, the exposure level (C) would be:

$$C = (E \times H \times LC \times ta + Su) \times D \times RPE \qquad (1)$$

The model simplifies the dispersion of contaminants away from sources using two notional spatial regions: the *near-field*, which is a volume around the worker whose exposure is being investigated and the *far-field*, which comprises the remainder of the work environment. Equation 1 should therefore more correctly be written with suffixes for the near-field, i.e. "NF" and where the source is in the far-field with "FF", as in equations 2 and 3.

$$C_{NF} = (E_{NF} \times H_{NF} \times LC_{NF} \times ta_{NF} + Su_{NF}) \times D_{NF} \times RPE \qquad (2)$$

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$$C_{FF} = (E_{FF} \times H_{FF} \times LC_{FF} \times ta_{FF} + Su_{FF}) \times D_{FF} \times RPE \quad (3)$$

In this scheme the intrinsic and passive emissions nominally have concentration units (fibres/ml). This would correspond to the airborne concentration generated with a certain 'standardised' handling. The other terms in these equations are dimensionless. Overall exposure (C) is the sum of the NF and FF exposure level terms, i.e.

$$C = C_{NF} + C_{FF} \quad (4)$$

To reconstruct exposure levels, the assessor must assign numeric values to each of the parameters. Selection of these parameters should be based on descriptive information for the process and work activities, although in some instances they may need to use their judgement, e.g. when details about the duration of the dust generating activity are unavailable or the task description is unclear. To aid consistency while coding exposure level it is recommend that assessors are trained and use the asbestos-specific guidance (see Supplemental Data 1), which also ensures estimates are obtained in units of fibres/ml. Exposures can be independently reconstructed by two or three assessors if there is a need for greater reliability, but there is little value in having more than three independent assessments (Semple et al., 2001).

In the present study we have used the method to estimate exposure for a number of scenarios selected from either the published literature or from in-house reports (Supplemental Data 2). In each case a text description of the scenario was extracted and this was used as the basis for the reconstruction. No allowance was made for the reduction in exposure from wearing a

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respirator because in each case the estimate was compared with measurements made outside any respiratory protection. A number of the scenarios were used in a previous study (Cherrie and Schneider, 1999). However, at the stage of assessment, the available measurement data were unknown to the assessor. The modelled data were input to a Monte Carlo simulation where the assigned parameters were varied from -50% to +50% of the value, selected from a uniform distribution. The simulation was carried out 1,000 times and the 5th and 95th percentile values were used as measures of the uncertainty in the assessment from parameter assignment.

Where the measurement data was only available as a summary range with the number of measurements, we used imputed values evenly spaced out on the log scale, e.g. 1, 3, 10 etc. We carried out a linear regression analysis of the log-transformed measurement (lnM) and modelled estimates (lnC) using 'regress' command in the STATA software package (Statacorp. 2013. Stata Statistical Software. Release 13. College Station, TX: Statacorp LP). The 'predict' command was used to calculate the linear predictor of the final model and the standard error of the forecast, the latter being used to derive upper and lower bounds on the forecast.

Results

There were 32 scenarios assessed, with between one and 23 measurements of inhalation exposure level available for each (median 5 measurements). For four scenarios only the mean and range of exposure levels were available. The average exposure measured for each scenario ranged from 0.001 fibres/ml (engine reassembly with the installation of new chrysotile asbestos-containing gaskets) to 226 fibres/ml (grinding and grit blasting on steel

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girders with crocidolite spray insulation). All measurements were made during the work tasks rather than as 8-hour average values.

The results of the assessments in comparison with the measured data are shown in Figure 1. The area of each circle is proportional to the number of measurements contributing to the scenario and the vertical lines represent the minimum and maximum model estimates derived from the Monte Carlo simulation of parameter uncertainty. The dotted line is the line of equality and the solid line is the regression line (shaded area is the 95% prediction? interval).

There is an apparent tendency of the model to overestimate at lower levels of exposure and under estimate at higher levels. The regression line ($C = 1.285xM^{0.705}$, $r^2=0.74$) is significantly different from the 1:1 line ($p<0.001$). The prediction interval, the interval around the regression line within which 95% of the measurements are located, is just over an order of magnitude higher or lower.

In a number of situations there was more than a ten-fold difference between the estimated value and the measured exposure level, e.g. in the scenario involving removal of asbestos-containing gaskets in a chemical plant (Supplemental Data 2, Scenario A31) where the assessment relied on the brief text description extracted from the published paper describing the work (Spence and Rocchi, 1996). The average measured value was 0.1 fibres/ml (range 0.051 – 0.24 fibres/ml) and the estimate was 0.002 fibres/ml (uncertainty range 0.001 – 0.005 fibres/ml). The text description for the task stated that when a gasket was removed, the individual applied a wetting agent to the gasket, and then attempted to remove it with little

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effort using only a putty knife. If the gasket came out easily, it was placed in a plastic bag for special disposal. If the gasket proved difficult to remove or broke in the process, it was left for a second group of workers to deal with. Workers removed between 2 and 9 gaskets in a shift, although there was no information about the time spent in removal. The main reasons for the low estimated exposure were the assumed low substance emission potential (E=0.2) and low activity emission potential (H=0.1), along with low time on task (ta=0.1). These parameters resulted in the low estimated value. However, the authors also noted that, 'on further analysis with transmission electron microscopy it was found that only four of the 11 samples contained asbestos in very low concentrations and that most of the fibres, which were identified using phase-contrast microscopy, probably originated from the glass fibre lagging around the pipes'.

Discussion

The model estimation method described here has the potential to reconstruct individual exposure to asbestos across a wide range of circumstances to within about an order of magnitude or the average of several periods of exposure more precisely. The estimates can be used to reconstruct cumulative exposure for multiple jobs and multiple tasks within a job by subdividing the work history into a sequence of tasks and then combining the data, weighting each task exposure by the total time worked in that task. The approach relies on descriptive information about the work process and the environment where the work was undertaken, which can be obtained by interview with the exposed person or a work colleague. As was the case in this exercise the information can be quite brief, but if more detail is available it is likely to result in more precise estimates. The method is suitable for use in epidemiological studies, for reconstructing exposure for civil litigation or compensation cases

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and potentially in selecting patients for future screening for chemoprophylaxis studies. The exposure determinants in the model define the key information that should be collected from interviews with exposed individual or others knowledgeable about their exposure. Assessors should be trained by someone experienced in the method and undertake suitable quality assurance assessments by reconstructing exposures for scenarios where measurement data are available. Using the mean of two or three independent assessors can reduce the variability in the final estimates (Semple et al., 2001) and in addition reconstructing exposure for a lifetime work history comprising several jobs would also result in reduced variability. Use of any available exposure measurement data, within a Bayesian framework, could improve the accuracy of the estimates further (McNally et al., 2014).

The data from this exercise are comparable with the information in Cherrie and Schneider (1999) with both assessments showing a high correlation between the log-transformed estimated and measured exposure concentrations, with an overall overestimation in the assessments. The association is most likely because of the interlinking of different model parameters between scenarios, e.g. if the substance emission potential for asbestos-containing materials with 10 – 15% chrysotile asbestos is set at 0.6 for one scenario then it should be the same of all other scenarios where the same material is used. The positive bias is either dependent on the descriptive information used to reconstruct the exposure or is an inherent part of the exposure assessment methodology. It has been observed with other exposure reconstruction methods involving subjective judgement that assessments are often positively biased, with the bias reduced when the assessors have access to contextually relevant measurement data (Hawkins and Evans, 1989).

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There are other approaches that have been proposed for estimating past exposure to asbestos. For example, Rasmuson et al., (2014) carried out a retrospective exposure assessment for 363 deceased asbestos workers for whom asbestos lung burden data were available (fibre number assessed by light microscopy and scanning electron microscopy plus number of asbestos bodies, both per gram wet lung). The exposure estimates were independently carried out by four experienced industrial hygienists using expert judgement, with the cumulative exposure estimated, i.e. as fibres/ml-years. Detailed information about the exposure circumstances was sparse, although the job title or exposure circumstances and duration of exposure were available for each case. The assessors showed a high degree of correlation on the assessed cumulative exposure (r^2 for log-transformed data between 0.81 and 0.88), which must, at least in part, reflect the given specific exposure durations. There was a statistically significant association between the average cumulative exposure estimates and the lung burden (r^2 = 0.45 for the log-transformed data). However, this method relies completely on the expertise of the assessors and is not easily generalizable.

Pannet et al., (1985) developed a job-exposure matrix (JEM) for a range of occupational carcinogens including asbestos, although in common with most tools of this type exposure was described as a categorical variable (high, moderate, low or none). Burdorf and Swuste, (1999) developed a JEM for asbestos with 19 jobs and exposure in five decades from 1946 to 1995, with exposure categorised into four exposure levels and four probability groups. The exposure estimates were to be used in a stepwise decision tree to help ascertain causation of asbestosis and mesothelioma. These approaches provide a relatively crude selection of individuals diagnosed with mesothelioma with a cumulative exposure above around 0.25 fibres/ml-years being identified as having their disease caused by asbestos. van Oyen et al.,

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(2015) developed a JEM for a wide range of jobs in Australia based on expert judgement supported by a wide range of historic exposure data, although the data were not quantitatively used to assess exposure (AsbJEM). Annual average exposure and asbestos type were estimated for this JEM for three time periods (1943–1986, 1987–2003, ≥2004).

Peters (2016a) describe a JEM developed for four carcinogens, including asbestos, based on statistical modelling of a large number of personal exposure measurements (27,958 for asbestos) and a prior categorical assessment of exposure (none, low and high). The statistical model allowed exposure estimates to be provided by job, subdivided by geographic region and year. While this approach has the benefit of being based on quantitative data it is dependent on these data being representative of the exposure circumstances, and for example it is notable that there is little contrast in the modelled exposure level between the three exposure categories (e.g. the geometric mean for low jobs was 0.061 fibres/ml and for high jobs 0.074 fibres/ml). There are also marked regional differences in estimated exposure (e.g. Germany and the Netherlands being a factor of 10 times higher than UK and Sweden), which is hard to explain by differences in legislation or work practices.

Most JEMs are primarily based on the judgement of the researchers with the assessment based on relatively broad job titles encompassing a diverse range of work involving asbestos, and none have been validated against objective measurement data; their reliability is therefore likely to be poor. Kottek and Kilpatrick (2016) criticised the Australian AsbJEM for underestimating the frequency of high exposure tasks, resulting in their view in considerably underestimated annual average exposures for some jobs, e.g. by more than an order of magnitude. In response, the authors (Peters et al., 2016b) highlighted the inherent limitation

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of JEMs that they assign exposure for all people with the same job title similarly, despite the likely very large variation in actual exposure within a job (Kromhout et al., 1993). While JEMs can provide estimates of past exposure, and they may be the only suitable approach where there is very limited information about the exposure circumstances, they are likely to be imprecise and inaccurate. The method outlined here defines the additional information beyond job title that should be collected to describe an exposure circumstance and provides specific individual estimates based on these data.

An important use for this exposure reconstruction method could be selection of past asbestos workers or others at increased risk of asbestos-related cancer for screening (lung cancer or mesothelioma) and/or trials of novel chemoprophylaxis strategies. Those who were exposed to asbestos in the past and their families are naturally often concerned about the risk of being diagnosed with an asbestos-related disease, and often call for screening to detect disease. This was recently reflected in the outcome of the James Lind Alliance Priority Setting Partnership (Stephens et al., 2015), which brought together patients, carers, researchers and clinicians involved with mesothelioma. Research Priority no. 9 stated 'does an annual chest x-ray and/or CT scan and medical examination in high-risk occupations (e.g. carpenters, plumbers, electricians, shipyard workers) lead to earlier diagnosis of mesothelioma?' The Helsinki Criteria group made a similar recommendation (Wolff et al., 2015). However, this question presupposes that chest x-ray/CT screening with an accompanying medical examination is a fruitful screening method, and that appropriate patients can be simply selected based on their occupation. Previous studies demonstrated this is not the case (Fasola et al., 2007; Roberts et al., 2009) and mesothelioma screening is likely to be complex area, with technological challenges in detecting a difficult to image cancer and ethical issues in

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detecting a cancer early, without curative treatment currently available. Nevertheless, it is widely accepted that earlier detection of cancer is likely, over time to improve outcomes, not least by allowing the maximum possible number of patients to enter clinical trials of new treatments. It is our view that, given the considerable expansion of mesothelioma research over recent decades, early detection will accelerate the development of new treatments and should be pursued aggressively. This view is clearly supported by patients (Stephens et al., 2015). In addition, an earlier mesothelioma diagnosis will facilitate improved access to the currently available therapies, including chemotherapy which improves survival in some patients (Santoro et al., 2008; Vogelzang, 2008; Zalcman et al., 2016). Other clinical services which can be provided to mesothelioma patents include medical thoracoscopy for optimal diagnostics (Hooper et al., 2010; Rahman et al., 2010), means of controlling pleural effusion (pleurodesis and indwelling pleural catheters (Fysh et al., 2013; Rintoul et al., 2014), admission avoidance clinics and access to a mesothelioma clinical nurse specialists (White, 2016) who can provide holistic care and advice about symptom control. In most healthcare systems these services are provided regionally and early detection allows patients to access these more easily.

Multiple research groups, including our own, are currently testing a range of novel biomarker technologies, including soluble proteins in blood (Creaney et al., 2014; Ostroff et al., 2012; Pass et al., 2012; Tabata et al., 2013) molecules in exhaled breath (Chapman et al., 2012; Dragonieri et al., 2012) and imaging end-points (Coolen et al., 2014; Tsim et al., 2015), allied to the asbestos exposure model described here could be used in the near future to test better screening strategies. However, screening will only be practicable and acceptable if the program can first identify those most at risk. This could be done by reconstructing the

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cumulative exposure of former asbestos workers or others at risk and using these data to estimate lifetime risk using a suitable risk model, such as that of Hodgson and Darnton (2000). Selecting individuals' whose lifetime risk is estimated to be more than about 5% would probably result in a viable pre-selection for screening, or enrolment in chemoprophylaxis programmes which are currently under development. Feasibility and pilot studies to test this approach are urgently needed.

Funding

No external funding was received.

Conflict of interest

JWC and DMcE have previously prepared reports for civil and criminal court cases involving exposure to asbestos.

Acknowledgements

We are grateful to our colleagues Professor Martie van Tongeren and Dr Alan Jones for their helpful comments on the draft manuscript.

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Figure title

Figure 1: Estimated and average measured exposure level for each scenario