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

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**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 estimates from the model was 0.86, and 95% of the estimated individual values were within 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 chemoprophylaxis.

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

1. 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 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 1980–2549 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-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 (Bertoglio and Waller, 2016) and hemi-thoracic radical radiotherapy (Rümmer 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.

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 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.

2. 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; Tielmans et al., 2008b) and for the Dutch control banding tool Staffenmanager (Tielmans 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 Tielmans 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 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 the 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:

\[ C = (E \times H \times LC \times ta + Su) \times D \times RPE \]  

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. Eq. (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 Eqs. (2) and (3).

\[ C_{NF} = (E_{NF} \times H_{NF} \times LC_{NF} \times ta_{NF} + Su_{NF}) \times D_{NF} \times RPE \]  

\[ C_{FF} = (E_{FF} \times H_{FF} \times LC_{FF} \times ta_{FF} + Su_{FF}) \times D_{FF} \times RPE \]  

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.
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