

Role of asbestos clearance in explaining long-term risk of pleural and peritoneal cancer: a pooled analysis of cohort studies

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ABSTRACT

Objectives Models based on the multistage theory of cancer predict that rates of malignant mesothelioma continuously increase with time since first exposure (TSFE) to asbestos, even after the end of external exposure. However, recent epidemiological studies suggest that mesothelioma rates level off many years after first exposure to asbestos. A gradual clearance of asbestos from the lungs has been suggested as a possible explanation for this phenomenon. We analysed long-term trends of pleural and peritoneal cancer mortality in subjects exposed to asbestos to evaluate whether such trends were consistent with the clearance hypothesis.

Methods We used data from a pool of 43 Italian asbestos cohorts (51 801 subjects). The role of asbestos clearance was explored using the traditional mesothelioma multistage model, generalised to include a term representing elimination of fibres over time.

Results Rates of pleural cancer increased until 40 years of TSFE, but remained stable thereafter. On the other hand, we observed a monotonic increase of peritoneal cancer with TSFE. The model taking into account asbestos clearance fitted the data better than the traditional one for pleural ($p=0.004$) but not for peritoneal ($p=0.09$) cancer.

Conclusions Rates of pleural cancer do not increase indefinitely after the exposure to asbestos, but eventually reach a plateau. This trend is well described by a model accounting for a gradual elimination of the asbestos fibres. These results are relevant for the prediction of future rates of mesothelioma and in asbestos litigations.

INTRODUCTION

Mathematical models based on the multistage model of tumour induction predict that rates of malignant mesothelioma continuously increase with time since first exposure (TSFE) to asbestos,

Key messages

What is already known about this subject?

- ▶ Classical mathematical models based on the multistage model of tumour induction predict that rates of mesothelioma continuously increase with time since first exposure (TSFE) to asbestos, even after the end of external exposure.
- ▶ However, the exact shape of the relationship between TSFE and mesothelioma risk is still a matter of debate, as very few studies provide sufficiently long enough follow-up to evaluate long-term trends.

What are the new findings?

- ▶ This question was investigated in one of the largest asbestos databases in the world, including more than 50 000 subjects from 43 different cohorts.
- ▶ The risk for pleural mesothelioma does not increase indefinitely after the exposure to asbestos, but eventually reaches a plateau, and this trend is well described by a model accounting for a gradual elimination of the asbestos fibres.

How might this impact on policy or clinical practice in the foreseeable future?

- ▶ These results are relevant for the prediction of future rates of mesothelioma and in asbestos litigations.

even after the end of external exposure, according to the following formula:

$$I_t = c(t - w)^k,$$

where I represents the incidence rate of mesothelioma t years after the exposure, c is the cumulative exposure, w is the lag time, the period following the exposure during which it is assumed that the



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incidence of mesothelioma does not increase, and k represents the number of stages (minus 1) needed to induce mesothelioma.¹²

Studies conducted in the 1970s and in the 1980s reported a good agreement between the predictions based on the model proposed by Newhouse and Berry (hereafter referred to as the traditional model) and the observed rates of mesothelioma in occupational cohorts.³ However, more recent studies,^{4–7} characterised by longer follow-up times, suggest that the incidence of mesothelioma might level off many years after the first exposure to asbestos. It has been suggested that such a plateau can be due to the observed gradual elimination of asbestos fibres from the lungs.^{8–10} For this reason, later on Berry¹¹ proposed an ‘elimination’ model,

$$I_t = c(t - w)^k \exp(-\lambda t),$$

where the asbestos clearance is modelled assuming an exponential decay of fibres. The exact shape of the relationship between TSFE to asbestos and risk of mesothelioma is still a matter of debate, as very few studies provide enough cases after 40 years of TSFE, the period after which the predictions of the two models start to diverge. To contribute to the evaluation of the ‘elimination’ model and therefore of the clearance hypothesis, we previously used data from an Italian occupational cohort characterised by a very long follow-up time. Results of this study suggested a possible effect of asbestos clearance on mesothelioma risk, but were based on small numbers.¹² In the present study, we replicated the analysis using data from a pool of 43 Italian asbestos cohorts.¹³ Cohorts included in this large database (51 801 workers) have very long follow-up times and include plants from different industrial sectors. This constitutes a unique opportunity for investigating long-term trends of mesothelioma. Specifically, we evaluated whether the elimination model fits the mortality data for pleural and peritoneal cancer better than the traditional model.

METHODS

Data collection

The characteristics of the pooled study are reported in detail elsewhere.¹³ Briefly, the study included data from 43 Italian asbestos cohorts. The industrial activities represented were asbestos cement (13 076 subjects), rolling stock (carriages and engines) construction and maintenance (23 810), shipyards (5120) and related activities (1170), glassworks (3727), harbour and dockyard workers (1939), and other industrial categories (882). Moreover, a cohort of Italian miners who worked at the crocidolite mine of Wittenoom, Australia (300 subjects) and a non-occupational cohort of asbestos-cement workers’ wives (1777) were included in the pool as well. For the purposes of the present analysis, we classified

the industrial activities in three groups: asbestos cement, rolling stock construction/maintenance and other activities. The cohorts included in this study were exposed to both chrysotile and crocidolite, with the exception of the Wittenoom miners who were exposed to crocidolite only. No cohort was exposed to chrysotile only.¹³

Follow-up of subjects and ascertainment of the causes of death were performed by the single research units that originally studied the participating cohorts. The registrar’s offices of the town of residence of the individuals were contacted to obtain information on vital status, using a procedure commonly used in Italian cohort studies.⁵ Causes of death were provided by the registries of the causes of death of the different local health authorities for deaths that occurred from 1986 onwards and by the registrar’s office of the municipality for deaths that occurred before 1986. The underlying cause of death was coded according to the International Classification of Diseases (ICD), 8th, 9th and 10th Revisions, according to the date of death. The end of follow-up was different among the included cohorts, but it was in any case successive to 31 December 2010, in order to grant a sufficient length of follow-up. Information about the subjects from the different cohorts was collected by each research unit. Anonymised data were then sent to the study coordinating centre. Pooled information included gender, birthdate, vital status, date of death/last observation, causes of death, and date of start and end for each period of employment. Quality control of data led to the exclusion of 2635 records (4.8% of the initial 54 436). The final pooled cohort included 51 801 individuals (46 060 men and 5741 women). Vital status was determined for 98.5% of the cohort, and the cause of death was identified for 95.0% of the dead subjects. At the end of follow-up, 22 045 subjects (42.6%) were dead, 28 987 (55.9%) alive and 769 (1.5%) lost to follow-up. The total number of person-years experienced from cohort members was 1 968 627 (table 1).

Statistical analysis

Rates of pleural and peritoneal cancer were modelled using the traditional and elimination model. Following the approach proposed in previous studies,^{7,12} the models were first log-transformed in the following way:

$$\log(\text{rate}_t) = \alpha + \beta_x X + \beta_1 \log(c) + k \log(t - w) \text{ (Traditional model)}$$

$$\log(\text{rate}_t) = \alpha + \beta_x X + \beta_1 \log(c) + k \log(t - w) + \lambda t \text{ (Elimination model)}$$

Table 1 Number of cases, mortality rates and person-years of observation for pleural and peritoneal cancer, stratified by time since first exposure to asbestos

Time since first exposure (years)	Cases of pleural cancer	Rate of pleural cancer (per 1000 person-years)	Cases of peritoneal cancer	Rate of peritoneal cancer (per 1000 person-years)	Person-years
≤19	23	0.02	4	0.004	954 899
20–24	27	0.12	6	0.03	234 328
25–29	71	0.33	11	0.05	215 717
30–34	113	0.61	15	0.08	186 072
35–39	137	0.93	25	0.17	147 644
40–44	116	1.16	30	0.30	99 677
45–49	128	1.93	32	0.48	66 378
50–54	77	2.14	23	0.64	35 987
At least 55	58	2.08	29	1.04	27 906
Total	750		175		1 968 627

where α , β_x , β_1 , k and λ were the coefficients to be estimated. In the models, α represents the log of the baseline rate, X is a vector of covariates included for adjustment (see hereafter) with their coefficients β_x , c is the cumulative exposure, t the number of years elapsed from the first exposure (TSFE), and w is the lag time. The two models were then analysed using standard methods for Poisson regression and were compared through likelihood ratio test. We did not set any constraint for the possible values of the coefficients. According to previous studies,^{12,14} we assumed a lag time of 5 years for both models. However, we also carried out sensitivity analyses varying the value of w between 0 and 10. To ensure non-negative rates for each value of TSFE, we set $(t-w)$ equal to 0 if $(t-w)$ was less than 0. TSFE to asbestos of the subjects was assumed to be equal to the time since entry in the cohort. As cumulative exposure was not available in this study, duration of employment was used as a proxy of it in the analysis. We included in the models duration of employment, industrial activity and an interaction term of the two. Both TSFE and duration of employment were entered in the models in years, as continuous variables.

Several secondary analyses were conducted to further evaluate the robustness of our estimates. We repeated the analysis stratifying by industrial activity and sex to evaluate the presence of heterogeneity. We also adjusted the results for calendar year, to take into account possible changes in diagnostic accuracy. Different authors suggest that predictions based on models based on the multistage theory of cancer can be inaccurate in very old people.^{15–17} For this reason, we rerun the analysis censoring subjects at 80 years of age. Finally, we evaluated the influence of individual cohorts on the overall results by excluding one cohort at a time (leave-one-out approach).

The results of the Poisson regressions were expressed in terms of estimated coefficients and 95% CIs. Statistical significance was set to 5% in bilateral tests. Analyses were performed with the Stata V.12 software.

RESULTS

Table 1 presents the distribution of the cases of pleural and peritoneal cancer and the person-years of observation by TSFE to asbestos in the pooled cohort. About 50% of pleural cancers and 65% of peritoneal cancers developed after 40 years of TSFE. Rates of pleural cancer increased until 40 years of TSFE, but remained stable thereafter. On the other hand, a monotonic increase was evident for peritoneal cancer through all the categories of TSFE (table 1).

A comparison of the results obtained from the elimination and the traditional models is reported in table 2. The elimination model fitted the data better than the traditional model ($p=0.004$) for pleural cancer but not for peritoneal cancer ($p=0.09$). The estimated value of k for pleural cancer was 2.02 and 3.28 in the

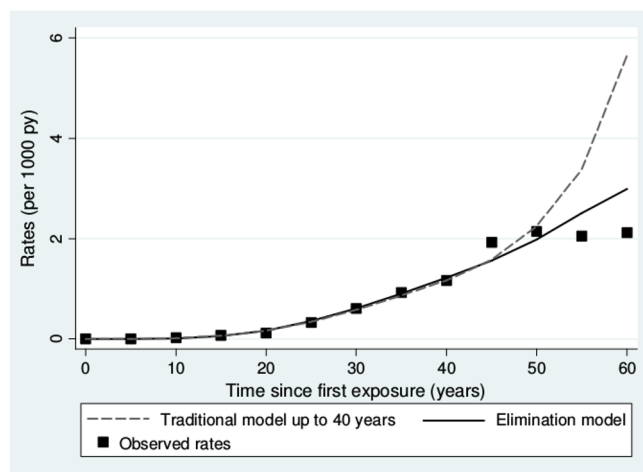


Figure 1 Observed and predicted rates of pleural cancer under different models, by time since first exposure. py, person-years.

traditional and in the elimination model, respectively. The elimination model estimated an asbestos clearance of 4% per year, corresponding to a half-life of 17 years.

Figure 1 shows the observed and predicted rates of pleural cancer under the traditional and the elimination models. The traditional model described the data well up to 40 years of TSFE, but grossly overestimated the rates thereafter. On the opposite, the elimination model was able to better describe the plateau observed in the last categories of TSFE.

Several secondary analyses were conducted to evaluate the robustness of the main analysis, but the results did not change appreciably. In particular, the estimated elimination rate for pleural cancer was consistent among the different industrial sectors (table 3) and between genders (for men: $\lambda=0.04$, 95% CI 0.01 to 0.08; for women: $\lambda=0.02$, 95% CI -0.04 to 0.08).

The results did not change either when we adjusted for calendar time, to take into account possible changes in diagnostic accuracy over time ($\lambda=0.05$, 95% CI 0.02 to 0.08) and when we censored subjects at 80 years of age ($\lambda=0.03$, 95% CI 0.00 to 0.07). Varying the values of the lag time in the models did not substantially change the results, with estimates of the elimination rate ranging between 0.03 and 0.07. Finally, the results did not change appreciably after the exclusion of one cohort at a time (leave-one-out method), with estimates of the elimination rate ranging between 0.04 and 0.06.

DISCUSSION

In an analysis based on 43 Italian asbestos cohorts, we found a plateau in the rates for pleural cancer many years after the start of exposure. We also showed that a model accounting for a gradual elimination of the fibres fits the data better than the traditional one, which instead predicts a continuous increase of rates over time.

Our results are consistent with those from previous studies that evaluated the elimination model. A previous study that some of us carried out in the Eternit cohort reported $\lambda=6\%$ per year for pleural cancer.¹² Berry and colleagues⁴ analysed the occurrence of mesothelioma in Wittenoom crocidolite miners and observed that the best fit was obtained by the model with $\lambda=15\%$ per year. This estimate confirmed a previous analysis published in 2004 using data from the same cohort.¹⁴ Reid and colleagues⁷ carried out a pooled analysis of mesothelioma mortality and incidence among eight

Table 2 Estimated parameter values and their 95% CI for pleural and peritoneal cancer in the elimination and traditional models

Models	Parameter	Pleural cancer	Peritoneal cancer
Elimination model	k	3.28 (2.29 to 4.27)	1.86 (0.30 to 3.44)
	λ (per year)	0.04 (0.01 to 0.07)	-0.04 (-0.09 to 0.01)
Traditional model	k	2.02 (1.62 to 2.42)	3.08 (2.19 to 3.98)
Likelihood ratio statistic		8.33	2.84
df		1	1
P value		0.004	0.09

Models adjusted for duration of employment, industrial sector and an interaction term of the two.

Table 3 Estimated parameter values and their 95% CI for the elimination model, stratified by industrial sector

Industrial sector	Cases	k	λ (per year)
AC	400	3.57 (2.10 to 5.04)	0.03 (0.00 to 0.07)
Railways	193	5.34 (3.01 to 7.67)	0.06 (-0.01 to 0.13)
Other	157	2.17 (-0.15 to 4.48)	0.02 (-0.05 to 0.09)

Models adjusted for duration of employment.

AC, Asbestos Cement.

cohorts from Italy and Australia including individuals exposed to amphibole fibres. The authors observed the best fit for pleural cancer with $\lambda=4\%$ per year.⁷ Other published studies, although did not formally compare the elimination and traditional models, reported results that are in line with the plateau of pleural cancer that we observed in our study. Both the cohorts of insulation workers of Selikoff and Seidman¹⁸ and the cohort of gas-mask workers of McDonald and colleagues⁶ show an increase in death rates for pleural cancer until 45 years of latency, followed by a plateau thereafter (figure 2). Similar results were observed in the British Asbestos Survey,¹⁹ reporting a decrease in mortality for mesothelioma after 50 years of TSFE. A reduction in the rates of mesothelioma has been suggested also by other authors, although the results were based on small numbers of cases.^{11 20 21}

Asbestos clearance is a plausible reason of the observed plateau in the rates of pleural cancer. We report here briefly the results of animal and human studies on the clearance of amphiboles, as cohorts in our pool were exposed either to mixed fibres or to amphiboles only. Different animal studies showed the elimination of amphiboles after exposure by inhalation.²²⁻²⁵ Moreover, different human studies investigated the relation between lung burden of asbestos fibres and time from the cessation of exposure. A reduction in amphiboles lung burden over time was observed in South African miners,¹⁰ in Australian crocidolite miners,²⁶ in shipyards and insulation workers exposed to amosite in the USA and Canada,⁹ and in former gas-mask workers in the UK.⁸ Estimated values for the half-life of amphiboles reported

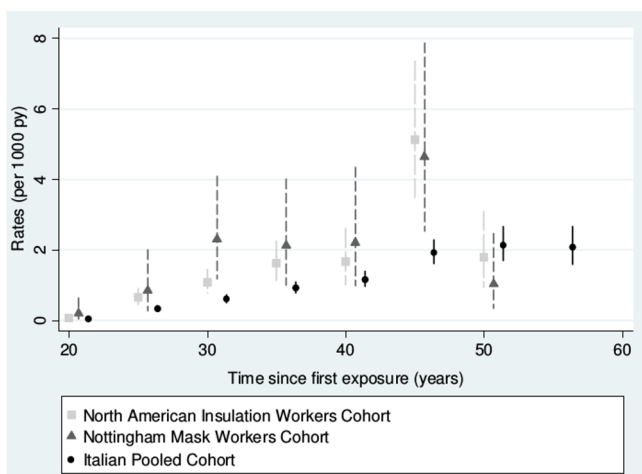


Figure 2 Observed rates and 95% CIs of pleural cancer in the Italian Pooled Cohort, in the North American Insulation Workers Cohort¹⁸ and in the Nottingham Mask Workers Cohort,⁶ against time since first exposure. Rates and CIs for the North American Insulation Workers Cohort and the Nottingham Mask Workers Cohort were estimated by the authors using data reported by Selikoff and Seidman¹⁸ and McDonald and colleagues.⁶ py, person-years.

in these studies, ranging between 6 and 20 years, are consistent with our results, suggesting a half-life of 17 years.

The possible role of fibre clearance in the development of peritoneal cancer remains unclear. Our results are consistent with those reported by Reid and collaborators,⁷ which estimated an elimination rate not statistically different from zero in their pooled analysis. In general, the few studies that evaluated long-term trends of peritoneal cancer reported a monotonic increase of this tumour over time, without any evidence of the plateau observed for pleural cancer.^{18 20} This different behaviour could be due to the route followed by the asbestos fibres to translocate to the peritoneum. Different authors suggest that most of the fibres reach the peritoneum through the lymphatics.^{27 28} In particular, diaphragm is extremely rich in lymphatics both on the pleural and peritoneal side that connect into a common submesothelial lacunar system, thus allowing the passage of fibres from the thoracic cavity to the abdomen.^{29 30} As most of the asbestos fibres are eliminated by the lung and the pleura through the lymphatics,^{28 31} it is possible that the clearance occurring at the thoracic level contributes to the translocation of the asbestos fibres to the peritoneum.

Levels of asbestos exposure could not be assessed in this study. Results of previous analyses on the same data suggest that exposure of the participants was substantial. Mortality rates for asbestosis, a good proxy of past asbestos exposure, were 300 times higher than expected.¹³ Such an increase was evident even for employees hired in 1970–1979, suggesting that the control of exposures was poor until the end of asbestos use in Italy.¹³ It is difficult to thoroughly evaluate how the use of duration as a proxy of cumulative exposure could have affected the results of our analysis. However, two pieces of information suggest that it is unlikely that this approach seriously biased our results. First, if it was the case, we should find a reduction of rates in the last categories of TSFE both for pleural and peritoneal cancer, as there is no reason to expect that misclassification of exposure acted differently on these two outcomes. In fact, very different trends were observed for pleural and peritoneal cancer, with a monotonic increase in the latter over time. Second, our results are consistent with those observed in the Wittenoom and gas-mask workers cohorts, where possible misclassification of exposure is not expected to be a major issue. Subjects in gas-mask workers cohort were characterised by a very short duration of exposure (maximum duration: 4 years; mean duration: 1 year) and quite homogeneous levels of exposure; hence, their cumulative exposures are expected to be similar.⁶ Regarding the Wittenoom cohort, cumulative exposure was available and was explicitly taken into account in the analysis.¹⁴

Our study is based on the assessment of mesothelioma from the death certificates reporting pleural or peritoneal malignancy as the underlying cause of death. Different authors suggest that the use of death certificates can determine an underestimation of mesothelioma occurrence.³²⁻³⁴ In particular, this misclassification of the outcome could have affected pleural cancers developed in old age, which in turn are expected to be more common in the last categories of TSFE. However, our results did not change when we provisionally excluded from the analysis subjects aged 80 years or more. Moreover, it should be noted that most of the deaths observed in the last categories of TSFE occurred in recent years, when the 10th revision of ICD, including a specific diagnostic code for mesothelioma, was already available. For this reason, possible misdiagnosis of mesothelioma is expected to be reduced in the last categories of TSFE. This phenomenon, if anything, is expected to produce an increase in the rates in such categories,

not the observed reduction. Finally, it is noteworthy that the pooled analysis of Reid and colleagues⁷ was able to compare results for incidence and mortality and did not observe relevant differences in trends with TSFE. Similar results were also obtained by the analysis of one of the cohorts included in the present study.⁵

A progressive attrition of the subjects at the highest risk in the cohort might explain the observed plateau in the mortality rates for pleural cancer. However, in this case a similar trend would be expected also for peritoneal cancer. For example, if heavy exposure to asbestos was expected to deplete the most vulnerable subjects from the cohort over time, this phenomenon would be expected to affect in a similar way pleural and peritoneal cancer, as they are both strongly associated to asbestos exposure. On the opposite, we observed a steady increase of the latter over time.

A direct consequence of the results of our study is that the predictions of future cases of pleural mesothelioma based on the traditional model could be overestimated.³⁵⁻³⁷ The difference between the predictions obtained by the different models can be substantial in some cases. Berry¹⁴ and colleagues showed the cumulative number of pleural mesothelioma predicted to occur in the Wittenoom cohort by 2020, according to the elimination model, was 50% lower than that predicted by the traditional model. For this reason we suggest to consider also the elimination model for the prediction of the future trends of the global mesothelioma epidemic. A second consequence of our results is that remote exposures to asbestos could have a lesser role in the development of pleural cancer than previously assumed. This can be of relevance in apportioning mesothelioma risk among multiple contributing sources of asbestos exposure during litigations.² Also in this case we recommend assuming a non-zero elimination rate in models used for this kind of calculations.

CONCLUSIONS

The results of our study confirm that rates for pleural cancer do not increase indefinitely after the exposure to asbestos, but eventually reach a plateau. This trend is well described by a model accounting for a gradual elimination of the asbestos fibres. The elimination model should be considered for the prediction of future mesothelioma incidence in the general population and for the apportionment of mesothelioma risk in litigations. Finally, we urge future epidemiological studies to analyse pleural and peritoneal cancer separately in order to thoroughly take into account their different time trends.

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Contributors FB-A: study design, planning and overview of data analysis, and drafting and critical revision of the article. DF: design of the study, data management, design and conduct of data analysis, and critical revision of the article. AA, MM, PP, AP, FC, SC, AB, LA, ER, FL, OS, CS, SM, EO, LM, GG, VB, VP, EM, EC: design of the study, conduct of the study and critical revision of the article. SS: exposure assessment and critical revision of the article. PG: design of the study and of data analysis and critical revision of the article. ST: data management and critical revision of the article. AR, TC: data management, data analysis and critical revision of the article. AM: design of the study, incidence data collection coordination and critical revision of the article. DM: design of the study, evaluation of exposure information and critical revision of the article. RP: design of the study, overview of mortality data analyses and critical revision of the article. CM: PI of the study, overview of the study and critical revision of the article.

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contracts representing the Italian Association of Cancer Registries (AIRTUM) for the preparation and publication of specific reports on the epidemiology of tumour pathologies with MSD, Lilly and Sanofi. All other authors declare they have no actual or potential competing financial interests.

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REFERENCES

- Newhouse ML, Berry G. Predictions of mortality from mesothelial tumours in asbestos factory workers. *Occup Environ Med* 1976;33:147–51.
- Price B, Ware A. Mesothelioma: risk apportionment among asbestos exposure sources. *Risk Analysis* 2005;25:937–43.
- Health effects Institute (HEI). Asbestos in public and commercial buildings: a literature review and synthesis of current knowledge. *Health Effects Institute - Asbestos research, Cambridge* 1991.
- Berry G, Reid A, Aboagye-Sarfo P, et al. Malignant mesotheliomas in former miners and millers of crocidolite at Wittenoom (Western Australia) after more than 50 years follow-up. *Br J Cancer* 2012;106:1016–20.
- Magnani C, Ferrante D, Barone-Adesi F, et al. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup Environ Med* 2008;65:164–70.
- McDonald JC, Harris JM, Berry G. Sixty years on: the price of assembling military gas masks in 1940. *Occup Environ Med* 2006;63:852–5.
- Reid A, de Klerk NH, Magnani C, et al. Mesothelioma risk after 40 years since first exposure to asbestos: a pooled analysis. *Thorax* 2014;69:843–50.
- Berry G, Pooley F, Gibbs A, et al. Lung fiber burden in the Nottingham gas mask cohort. *Inhal Toxicol* 2009;21:168–72.
- Churg A, Wright JL. Persistence of natural mineral fibers in human lungs: an overview. *Environ Health Perspect* 1994;102 Suppl 5:229–33.
- Du Toit RS. An estimate of the rate at which crocidolite asbestos fibres are cleared from the lung. *Ann Occup Hyg* 1991;35:433–8.
- Berry G. Models for mesothelioma incidence following exposure to fibers in terms of timing and duration of exposure and the biopersistence of the fibers. *Inhal Toxicol* 1999;11:111–30.
- Barone-Adesi F, Ferrante D, Bertolotti M, et al. Long-term mortality from pleural and peritoneal cancer after exposure to asbestos: possible role of asbestos clearance. *Int J Cancer* 2008;123:912–6.
- Ferrante D, Chellini E, Merler E, et al. Italian pool of asbestos workers cohorts: mortality trends of asbestos-related neoplasms after long time since first exposure. *Occup Environ Med* 2017;74:887–98.
- Berry G, et al. Malignant pleural and peritoneal mesotheliomas in former miners and millers of crocidolite at Wittenoom, Western Australia. *Occup Environ Med* 2004;61:14e–14.
- Cook PJ, Doll R, Fellingham SA. A mathematical model for the age distribution of cancer in man. *Int J Cancer* 1969;4:93–112.
- Moolgavkar S, Krewski D, Schwars M, et al. Mechanisms of carcinogenesis and biologically based models for estimation and prediction of risk. In: Moolgavkar S, Krewski D, Zeise L, et al, eds. *Quantitative estimation and prediction of human cancer risk*. Lyon: IARC press, 1999: 179–237.
- Pompei F, Polkanov M, Wilson R. Age distribution of cancer in mice: the incidence turnover at old age. *Toxicol Ind Health* 2001;17:7–16.
- Selikoff IJ, Seidman H. Asbestos-associated deaths among insulation workers in the United States and Canada, 1967–1987. *Ann N Y Acad Sci* 1991;643:1–14.
- Harding AH, Frost G. *The asbestos survey. Mortality among asbestos workers 1971–2005*. Prepared by health and safety laboratory for the health and safety executive. HSE books, 2009. Available: <http://www.hse.gov.uk/research/rrpdf/rr730.pdf> [Accessed 28 Jul 2017].
- Pira E, Pelucchi C, Buffoni L, et al. Cancer mortality in a cohort of asbestos textile workers. *Br J Cancer* 2005;92:580–6.
- Seidman H, Selikoff IJ, Gelb SK. Mortality experience of amosite asbestos factory workers: dose-response relationships 5 to 40 years after onset of short-term work exposure. *Am J Ind Med* 1986;10:479–514.
- Bellmann B, Muhle H, Pott F, et al. Persistence of man-made mineral fibres (MMMF) and asbestos in rat lungs. *Ann Occup Hyg* 1987;31:693–709.
- Eastes W, Hadley JG. A mathematical model of fiber carcinogenicity and fibrosis in inhalation and intraperitoneal experiments in rats. *Inhal Toxicol* 1996;8:323–43.
- Hesterberg TW, Chase G, Axten C, et al. Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. *Toxicol Appl Pharmacol* 1998;151:262–75.
- Musselman RP, Miller WC, Eastes W, et al. Biopersistence of man-made vitreous fibers and crocidolite fibers in rat lungs following short-term exposures. *Environ Health Perspect* 1994;102 Suppl 5:139–43.
- de Klerk NH, Musk AW, Williams V, et al. Comparison of measures of exposure to asbestos in former crocidolite workers from Wittenoom gorge, W. Australia. *Am J Ind Med* 1996;30:579–87.
- Kurimoto R, Kishimoto T, Nagai Y, et al. Malignant peritoneal mesothelioma: quantitative analysis of asbestos burden. *Pathol Int* 2009;59:823–7.
- Uibu T, Vanhala E, Sajantila A, et al. Asbestos fibers in para-aortic and mesenteric lymph nodes. *Am J Ind Med* 2009;52:464–70.
- Li J, Zhao Z, Zhou J, et al. A study of the three-dimensional organization of the human diaphragmatic lymphatic lacunae and lymphatic drainage units. *Ann Anat* 1996;178:537–44.
- Miserocchi G, Sancini G, Mantegazza F, et al. Translocation pathways for inhaled asbestos fibers. *Environ Health* 2008;7:1–8.
- Donaldson K, Murphy FA, Duffin R, et al. Asbestos, carbon nanotubes and the pleural mesothelium: a review and the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma. *Part Fibre Toxicol* 2010;7:5–17.
- Ferrante P, Mastrantonio M, Uccelli R, et al. [Pleural mesothelioma mortality in Italy: time series reconstruction (1970–2009) and comparison with incidence (2003–2008)]. *Epidemiol Prev* 2016;40:205–14.
- Kopylev L, et al. Monte Carlo analysis of impact of underascertainment of mesothelioma cases on underestimation of risk. *Open Epidemiol J* 2011;4:45–53.
- Roberti S, Merler E, Bressan V, et al. Malignant mesothelioma in the Veneto region (north-east of Italy), 1988–2002: incidence, geographical analysis, trends and comparison with mortality. *Epidemiol Prev* 2007;31:309–16.
- Hodgson JT, McElvenny DM, Darnton AJ, et al. The expected burden of mesothelioma mortality in Great Britain from 2002 to 2050. *Br J Cancer* 2005;92:587–93.
- Marinaccio A, Montanaro F, Mastrantonio M, et al. Predictions of mortality from pleural mesothelioma in Italy: a model based on asbestos consumption figures supports results from age-period-cohort models. *Int J Cancer* 2005;115:142–7.
- Pelucchi C, Malvezzi M, Vecchia CL, et al. The mesothelioma epidemic in Western Europe: an update. *Br J Cancer* 2004;90:1022–4.