The Royal College of Pathologists
Pathology: the science behind the cure

Guidelines on autopsy practice

Industrial/occupational-related lung disease deaths including asbestos

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Series authors: Dr Michael Osborn, Imperial College Healthcare NHS Trust
Professor Jim Lowe, Nottingham University Hospitals NHS Trust

Specialist authors: Dr Richard Attanoos, Cardiff & Vale University Health Board and Cardiff University
Dr Allen Gibbs, Cardiff & Vale University Health Board

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Produced by	The specialist content of this guideline has been produced by Dr Richard Attanoos and Dr Allen Gibbs, from University Hospital of Wales, and Cardiff University, Cardiff. The authors are recognised national and international experts in industrial lung disease, author/editors of two books and over 200 papers, members of the United States ï Canadian Mesothelioma Panel, International Mesothelioma Panel and College of American Pathologists and Pulmonary Pathology Society (CAP-PPS) Asbestosis Guidelines Committee.
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Comments	In accordance with the Collegeôs pre-publication policy, this document was on The Royal College of Pathologistsôwebsite for consultation from 17 January to 17 February 2017. This document replaces earlier editions and is part of the ôGuidelines on autopsy practiceôseries. **Dr Lorna Williamson** **Director of Publishing and Engagement**

The Royal College of Pathologists
4th Floor, 21 Prescot Street, London. E1 8BB
Tel: 020 7451 6700
Web: www.rcpath.org

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Contents

Foreword

The autopsy guidelines published by The Royal College of Pathologists (RCPath) are guidelines that enable pathologists to deal with non-forensic Coronerôs post mortems in a consistent manner and to a high standard. Guidelines are systematically developed statements to assist the decisions of practitioners and are based on the best available evidence at the time the document was prepared. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

The guidelines themselves constitute the tools for implementation and dissemination of good practice.

The stakeholders consulted for this document were:

- the Human Tissue Authority and its Histopathology Working Group, which includes representatives from the Association of Anatomical Pathology Technology, Institute of Biomedical Science, The Coroners Society of England and Wales, the Home Office Forensic Science Regulation Unit and Forensic Pathology Unit and the British Medical Association
- United Kingdom Pulmonary Pathology Club.

The information used to develop this guideline was derived from recent publication review and has been graded using modified SIGN guidance (see Appendix A).

No major organisational changes or cost implications have been identified that would hinder the implementation of the tissue pathways.

A formal revision cycle for all guidelines takes place on a five-year cycle. The College will ask the authors to consider whether or not the guideline needs to be revised. A full consultation process will be undertaken if major revisions are required. If minor revisions or changes are required, a short note of the proposed changes will be placed on the College website for two weeks for membersô attention. If members do not object to the changes, the short notice of change will be incorporated into the guideline and the full revised version (incorporating the changes) will replace the existing version on the College website.

The guideline has been reviewed by the Clinical Effectiveness Department, Death Investigation Group, Pulmonary Sub-specialty Advisory Group and Lay Governance Group. It has been placed on the College website for consultation with the membership from 17January to 17 February 2017. All comments received from the membership will be addressed by the authors to the satisfaction of the Director of Publishing and Engagement.

This guideline was developed without external funding to the writing group.

The College requires the authors of guidelines to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness Department and are available on request. The authors of this document have declared that there are potential conflicts of interest. Both authors have served as medical experts in asbestos injury claims for claimants and defendants.

1 Introduction

The purpose of this document is to provide guidance to the pathologist on the handling of industrial/occupational cases which include potential asbestos-related deaths and those relating to exposures to silica and coal.

The patterns of occupational exposures and consequently disease have changed over time.[1] Pneumoconioses relating to heavy dust exposures are now less commonly encountered when compared with industrial cancer deaths. The rates of malignant mesothelioma are still increasing in most countries, including the United Kingdom, set to reach a peak incidence of around 2500 cases per year until the end of the decade before decreasing.[2,3]Coal workersô pneumoconiosis and silicosis are now relatively uncommon as industrial causes for death.

It is recognised that variations exist in local coronial practice in industrial lung disease settings, particularly in the requirement for autopsy in persons with suspected malignant mesothelioma.

The levels of evidence reflect a combination of recommended good practice points based on the clinical experience of the authors, and extrapolated analysis of industrial lung disease studies.

1.1 Target users of this guideline

The target primary users of this guideline are practising consultant pathologists and pathologists in training, particularly those approaching the Certificate of Higher Autopsy Training (CHAT) examination and the FRCPath Part 2 in Forensic Pathology. The recommendations will also be of value to coroners to assist with inquests and solicitors handling personal injury claims in potential industrial-related deaths.

2 Role of the autopsy

- To describe and diagnose all occupational/industrial disease manifestations
- To determine the aetiology
- To determine the extent and severity of any other disease present (that would affect life expectancy or quality). This will be taken into account in assessing compensation if death is deemed to be due to a prescribed occupational/industrial disease.

[Level of evidence: D – The evidence has been taken from GPPs, published texts and extrapolated from non-analytic studies.]

3 Pathology encountered at the autopsy

Macroscopic examination: disease by claimed aetiological agent.

Asbestos:

- pleural plaques
- diffuse pleural fibrosis (uni- or bilateral, lower zone, >5 mm thick, >one third of lung)
- rounded atelectasis
- diffuse interstitial fibrosis
- malignant mesothelioma, pleura, peritoneum, pericardium, gonads
- lung carcinoma
- cutaneous corns.

Silica:

- nodular fibrosis ócclassical silicosisô
- progressive massive fibrosis ócomplicated silicosisô
- acute silicoproteinosis
- mixed dust fibrosis: silica plus inert/weak fibrogenic dust
- lung carcinoma candle-wax lesions.

Coal:

- simple coal workersôpneumoconiosis
  - ï primary dust macules (impalpable)
  - ï secondary dust nodules (palpable)
  - ï diffuse interstitial fibrosis.
- complicated coal workersôpneumoconiosis
  - ï progressive massive fibrosis (lesions >1 cm).
- coal dust tattoos
- diffuse interstitial fibrosis.

[Level of evidence: B.]

4 Specific health and safety aspects

Subjects with silicosis are at increased risk of tuberculosis.

[Level of evidence: B.]

No other aspects beyond standard health and safety standards.

[Level of evidence: GPP.]

5 Clinical information relevant to the autopsy

- Circumstances of death: this will assist in the assessment of the cause of death and the contribution, if any, of the claimed industrial agent.
- Past medical history: this will assist in the assessment of the cause of death and the contribution, if any, of the claimed industrial agent. Confounding factors such as tobacco smoking history can impact on the pathology assessment of asbestos lung cancer and lung fibrosis/asbestosis claims. History of connective tissue disease can confound the interpretation of industrial lung fibrosis claims. These factors are largely discussed in the section below.
- The medical records and often witness statements are required to detail the occupational and environmental exposure histories. For causation purposes, it is important to know:
  - ï the date of the first and last exposure to the claimed aetiological agent(s)

- ï job details and employment histories, including complete chronological job details and/or other exposures (para-occupational/domestic; environmental; ambient); this allows for the assessment of cumulative dust exposure (intensity and duration)
- ï for chronic fibrotic and neoplastic conditions, exposures less than 15 years prior to death are unlikely to be related to that putative or claimed aetiological agent.

- Social history and hobbies are important in cases of extrinsic allergic bronchiolo-alveolitis/hypersensitivity pneumonitis.
- In lung cancer cases, the smoking history should be identified, as tobacco is a recognised cause of most cases.
- In diffuse interstitial fibrosis (DIF) cases, clinical history and course is important. Idiopathic pulmonary fibrosis with usual interstitial pneumonia is a fast tempo condition, whereas other diffuse interstitial fibroses/pneumoconioses are not in general. This is reflected in the differing pathology.

[Level of evidence: B, C, D and GPP.]

6 The autopsy procedure

Complete post-mortem examination with the lungs handled according to the standard text guidelines.[1,4] A limited post mortem confirmed to examination of the thoracic cavity is considered sub-optimal.

[Level of evidence: GPP.]

7 Specific significant organ systems

Organ	Pathology	Agent
Skin	Linear tattoos	Coal
	Corns (knuckles, finger tips)	Asbestos
Thorax/lungs	Adult respiratory distress syndrome (shock lung)	Smoke, fumes
	Emphysema	Coal
	Macules	Coal, silicates, iron
	Nodular fibrosis	Coal, silica Silicate (talc, mica)
	Progressive massive fibrosis	Coal, silica, silicates
	Diffuse interstitial fibrosis, lower zone predominant	Asbestosis
	Diffuse interstitial fibrosis, upper zone predominant	Coal (rare) Silica Aluminium Beryllium
	Carcinoma	Asbestos, silica

Thorax/pleura	Plaques	Asbestos
	Nodular fibrosis	Silica
	Diffuse fibrosis	Asbestos
	Mesothelioma	Asbestos
Peritoneum and gonads	Mesothelioma	Asbestos (weak epidemiologic association in females)[5] and in gonadal mesotheliomas
Pericardium	Mesothelioma	Asbestos*(weak epidemiologic association)

8 Organ retention

- For tumour-related occupational deaths: lung (tumour and contralateral lung background), pleura, pericardium, peritoneum (if mesothelioma)
- For non-tumour cases: extensive sampling of lung parenchyma to determine extent and distribution as well as causation of fibrosis/other pathology
- For tumour (lung cancer or mesothelioma) ï at least three 8 cm^3 samples
- For background lung ï five 8 cm^3 samples from each lung (see Section 9).

It is not essential to retain whole organs, sagittal slices or adequately sampled tissue will suffice for purposes of diagnostic and causation.

Where there is the possibility of a legal claim for compensation, for example following an individualôs death from an industrial disease, tissue samples may be held by the solicitor representing the deceasedôs family. Where this is the case, the cause of death will already have been established and the material will then be being stored, with the knowledge and consent of the family, for a use other than a scheduled purpose under the Human Tissue Act. Therefore, the premises where the samples are kept do not need to be licenced by the Human Tissue Authority. However, storage on HTA-licenced premises is recommended where possible, as this helps to ensure traceability. It is recommended that the time for tissue retention be at least 5 years to allow for the slow passage of medicolegal cases.

9 Recommended blocks for histological examination – best practice

- If mesothelioma ï tumour (at least two random areas avoiding necrotic tumour): immunohistochemistry essential in undiagnosed cases, incorporating a pan-cytokeratin plus two epithelial and two mesothelial markers in line with International Mesothelioma Interest Group guidelines[6]
- If lung cancer ï tumour (at least three random avoiding necrotic tumour)
- In non-tumour-related occupational deaths: lung (a minimum of five tissue blocks required from each lung: upper lobe, apex; upper lobe, base, mid zone/middle lobe, upper aspect lower lobe and lung base) to determine extent, distribution and causation. (Optimal tissue blocks = 10 incorporating both all the above regions with representation of both peripheral and deep alveolated lung parenchyma)
- A modified grading schema of the College of American Pathologists using a four-point system is advocated.[7,8]
  - Grade 0 No fibrosis (or fibrosis limited to bronchiolar regions only)

- Grade 1 Bronchiolar wall plus involvement of first tier alveolar dust fibrosis
- Grade 2 First and second tier alveolar duct fibrosis. No bridging fibrosis
- Grade 3 Bridging fibrosis between acinar units
- Grade 4 Honeycomb lung

- The optimal availability of tissue is useful if mineral analysis is warranted (see below)
- Other organs: determined by macroscopic findings.

[Level of evidence: D and GPP.]

10 Other samples required

Three 8 cm^3 samples of lung (contralateral lung in tumour deaths) retained for mineral fibre analysis[9] ï this is for potential asbestosis, lung cancer and pleural mesothelioma cases (the latter only where there is no clear exposure history). Peritoneal mesotheliomas and mesotheliomas arising in women are increasingly reported with no clear exposure history so consideration for mineral analysis is relevant in these cases. (Note: Mineral fibre analysis can be undertaken on paraffin embedded or fresh lung tissue samples. Optimal results are generated from utilising multiple (3) tissue blocks or preferably from wet formalin fixed lung sampled from apex, base of upper lobe and base of lung as 2x2x2 cm cubes of tissue. Background lung devoid of macroscopic pathology yields best results, i.e. avoid tumour, pneumonia, infarction, etc.)

- Fibre analysis is applicable in cases of potential/claimed:
  - **asbestosis** (where cases are benchmarked against the asbestosis range)
  - This applies if light microscopic asbestos body counts are low or absent i.e. an average rate of $\geq$2 asbestos bodies per 1 cm^2 lung section area determined by routine thickness Perls stained section at 400x magnification. Thick unstained sections, wet lung ósqueezeôsamples and routine H&E sections are all inappropriate methods to undertake semi-quantitative ferruginous body counting in the evaluation of asbestosis.
  - **lung cancer ex asbestosis** (where cases are benchmarked against the asbestosis range)
  - pleural **malignant mesothelioma with no exposure history**
  - Extrapleural mesotheliomas and mesotheliomas in women.
- Recommendations for mineral analysis are that it is performed by electron microscopy (either by transmission or scanning mode) in an established laboratory with current controls (established for non-occupational persons) and for populations of subjects with asbestosis.[2]
- Mineral analysis performed by light microscopic methods do not allow for qualitative assessments because asbestos cannot be distinguished from non-asbestos fibres, and low optical resolution results in the majority of fibres being undetected. With heavy industrial exposures now significantly diminished the most sensitive and specific methodology is required to best evaluate potential industrial lung disease cases.
- Electron microscopic mineral analytic methods are considered essential for the full quantitative and qualitative evaluation of industrial/occupational diseases
- In medicolegal cases lung tissue should be retained ideally until the Court or Coroner/Fiscal completes their investigations ï a 5 year period is recommended

- Non-fibrous mineral analysis is advocated in cases of potential/claimed industrial silica, silicate (talc, mica, kaolin) or other specific exposures e.g. A metal analysis.

[Level of evidence: D and GPP.]

11 The clinicopathological summary

- Document gross/histological findings relating to occupational/industrial lung disease
- Correlate exposure history from clinical records/witness statements with pathological findings
- Determine significance of mineral fibre analysis if performed
- Document other concurrent pathology
- Determine cause of death.

12 Specific cause of death opinions/statements

All causes of industrial lung disease death must be correlated with the available clinical, imaging and autopsy data.

For causal attribution of asbestos-related disease including mesothelioma, asbestosis and lung cancer, there have been published guidance texts that have been supported and criticised.[2,7,8,10,11.]

It is recognised that there is no evidence to support the view that ambient exposures to asbestos from urban dwelling cause disease. The scientific evidence correlating cumulative exposure to asbestos and disease is established in occupational settings which are orders of magnitude above background ambient exposure levels. The evaluation of the significance of any exposure is determined by a consideration of cumulative dose and factors of fibre type (amphiboles versus chrysotile; fibre dimensional characteristics ï fibre length and width).

Not all asbestos is the same. Amphiboles and serpentines have different physical, chemical and biological factors which underpin their different toxicities in tissues. Amphiboles are 100ï 500 times more potent in the induction of mesothelioma than chrysotile on a fibre: fibre basis[12].The fibre potency difference is less marked for lung cancer 10ï 50:1; amphiboles: chrysotile. Amphiboles are far more bio-persistent than chrysotile. Chrysotile fibres are cleared rapidly from the lungs whereas amphibole persist for decades. Mineralogical studies correlated asbestos related disease with retention of amphiboles, not chrysotile.

In general, from a pathologistôs perspective, for malignant mesothelioma, after the diagnosis is confirmed and there is consideration of an appropriate latency (15 years) then the presence of concurrent asbestos-related pathology such as pleural plaques or the identification of asbestos bodies in lung tissue is sufficient for a causal attribution to asbestos, on a balance of probabilities. However, in some cases of asbestos-related mesothelioma, pleural plaques and asbestos bodies are not seen. In this circumstance, mineral analysis may be used to support prior exposure to amphibole asbestos. A substantiated occupational exposure history is important in many mesothelioma cases.

In general, from a pathologistôs perspective, for lung cancer attribution to asbestos, after the diagnosis of lung cancer is confirmed and there is consideration of an appropriate latency (15 years) then the presence of either pathological degrees of asbestosis (as set out in the CAP-PPS asbestosis guidelines report) or (in the absence of asbestosis) a asbestos fibre count within the range for asbestosis. The asbestosis range must be determined by electron

microscopic methods (as light microscopic methods are insensitive in inaccurate). The asbestosis range is reliant on the assembly of confirmed asbestosis cases in which qualitative and quantitative fibre data is available and the former refers to the total retained *amphibole* asbestos fibre content. The lower range value of the asbestosis range is the 5th percentile of fibre counts within the range.[8]

A fibre count below the asbestosis range or within the background control reference range for urban dwelling persons does not support a causal attribution of asbestos to the lung cancer.

There is a recognised synergism between smoking and asbestos in increasing lung cancer risk and this synergistic interaction is dependent on fibre type and industrial exposure. In most cases the synergism is between super-additive and sub-multiplicative.

The presence of pleural plaques represent an insufficient basis to causally attribute either a lung cancer or lung fibrosis to asbestos even on a probabilistic basis.

In general, from a pathologistôs perspective, for lung fibrosis attribution to asbestos i.e. for asbestosis, provision of an appropriate latency (15 years) plus the presence of lung fibrosis of appropriate pattern ï acellular and collagenous rather than fibroblastic and inflammatory (pathological criteria as set out in the CAP-PPS asbestosis guidelines[8]) with appropriate numbers of ferruginous bodies as determined by light microscopy (i.e. >2 asbestos bodies per 1 cm^2 lung section area determined by routine thickness Perls stained section at 400x magnification. or an asbestos fibre count within the range for asbestosis.

Usual interstitial pneumonia typical of idiopathic pulmonary fibrosis is not a characteristic feature of asbestosis. When seen in putative cases of asbestosis, IPF should be favoured.[13] There is presently a legitimate debate as to whether the presence of UIP excludes the diagnosis of asbestosis irrespective of asbestos body or fibre counts. Nonetheless the vast majority of UIP cases show no dose response relationship with asbestos.

For coal workersôpneumoconiosis and silicosis, clinical correlation is important to determine causation. The presence of anthracotic change and silicotic nodules in lymph nodes should not be interpreted to represent pneumoconiosis. Heavy coal dust exposures frequently coexist with emphysema in non-smokers and this can can cause respiratory impairment. However, simple coalworkers pneumoconiosis is unlikely to cause death unless complicated by pneumonia or severe emphysema with heart failure. Complicated coal workers pneumoconiosis with progressive massive fibrosis (PMF) can cause respiratory failure and death. This condition is now uncommon.[14]

Silica exposure without silicosis represents insufficient basis to attribute a lung cancer to silica exposure[15]. The presence of silicotic nodules in lymph nodes should not be interpreted as silicosis. An electron microscopic non-fibrous mineral analysis is useful to support a diagnosis of silica or silicate(kaolin, mica, talc) pneumoconioses or to determine specific exposures ï metals.

[Level of evidence: D]

For examples of death formulation, the following are provided:

1a. Malignant pleural mesothelioma

1b. Asbestos exposure

1a. Lung carcinoma

1b. Asbestos exposure

1a. Bronchopneumonia

1b. Asbestosis

1a. Progressive massive fibrosis (complicated coal workersôpneumoconiosis)

1a. Primary lung carcinoma

1b. Silicosis

1c. Silica exposure

[Level of evidence: GPP.]

13 Criteria for audit

The following standards are suggested criteria that might be used in periodic reviews to ensure a post-mortem report for coronial autopsies conducted at an institution comply with the national recommendations provided by the 2006 NCEPOD study (www.ncepod.org.uk/2006Report/Downloads/Coronial Autopsy Report 2006.pdf).

- Supporting documentations:
  - standards: 95% of supporting documentation was available at the time of the autopsy
  - standards: 95% of autopsy reports documented are satisfactory, good or excellent.
- Reporting internal examination:
  - standards: 100% of the autopsy report must explain the description of internal appearance
  - standards: 100% of autopsy reports documented are satisfactory, good or excellent.
- Reporting external examination:
  - standards: 100% of the autopsy report must explain the description of external appearance
  - standards: 100% of autopsy reports documented are satisfactory, good or excellent.

A template for coronial autopsy audit can be found on the RCPath website: www.rcpath.org/profession/clinical-effectiveness/quality-improvement/clinical-audit-templates.html

14 References

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15 Diseases Associated with Exposure to Silica and Nonfibrous Silicate Minerals. Silicosis and Silicate Disease Committee. *Arch Pathol Lab Med* 1988;112:673ï 720.

Appendix A Summary table – Explanation of grades of evidence

(modified from Palmer K *et al. BMJ*2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target type or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-controller cohort studies and high-quality case-controller cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target type or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-controller cohort studies and high-quality case-controller cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target type or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix B AGREE II compliance monitoring sheet

The guidelines of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this tissue pathway that indicate compliance with each of the AGREE II standards are indicated in the table below.

AGREE II standard	Section of guideline
Scope and purpose	
1 The overall objective/s of the guideline is/are specifically described	Foreword
2 The health question/s covered by the guideline is/arespecifically described	Foreword, 1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12 There is an explicit link between the recommendations and the supporting evidence	2ï 12
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2ï 12
16 The different options for management of the condition or health issue are clearly presented	Foreword
17 Key recommendations are easily identifiable	2ï 12
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	2ï 12
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	13
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword