Maladies de l'amiante:

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Avec la collaboration de P. Dumortier (minéralogiste),
M. Remmelink (AP), J.Thimpont (MT) and P.A.Gevenois (RX)

- Asbestos and asbestos exposure
- Mineralogical analysis

- Asbestos-related diseases
- Asbestosis and benign pleural diseases

- Mesothelioma
- Diagnosis, biomarkers, treatment

- Medico-legal aspects (FMP,FA)

- Conclusion and perspectives

Asbestos minerals

Industrial Use

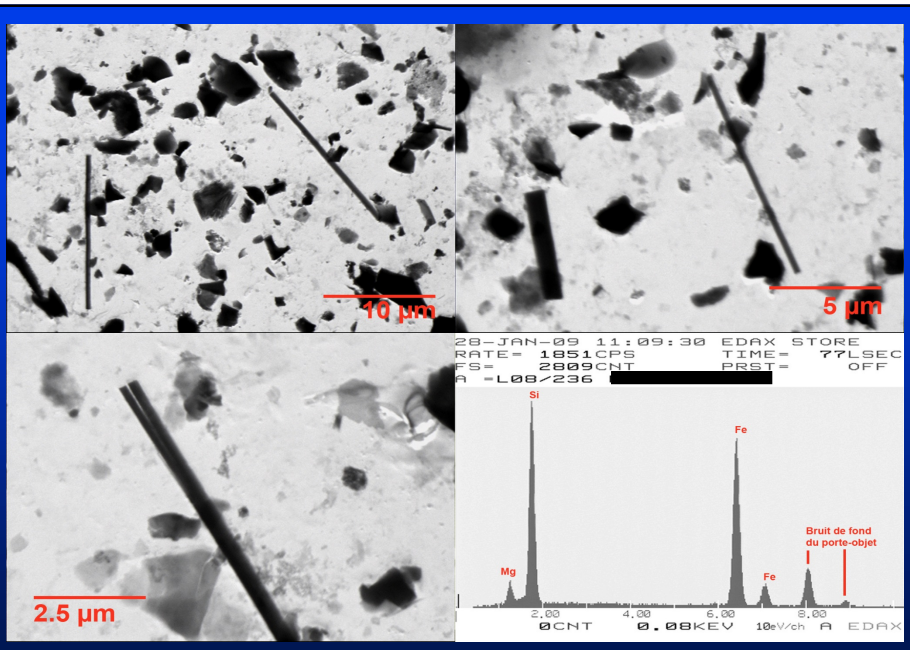
Common

Marginal

None

ASBESTOS

- ***Serpentine***
  - **Chrysotile** (White Asbestos) — Common
- ***Fibrous Amphiboles***
  - **Amosite** (Brown Asbestos) — Common
  - **Crocidolite** (Blue Asbestos) — Common
  - **Anthophyllite** — Marginal
  - **Tremolite** — None
  - **Actinolite** — None



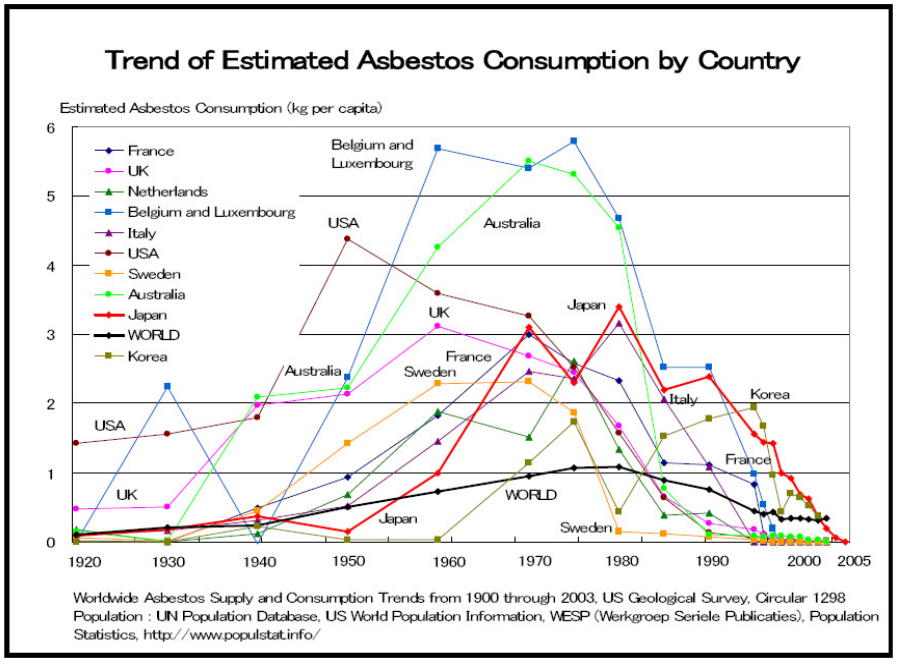
Electron microscopy views and energy dispersive x-ray spectrum of amosite fibers in BALF .

Major uses of asbestos

- Asbestos-cement products (pipes, tiles, plates)

- Friction materials (brake linings)
- Insulation (heat, cold, acoustical..)
- Fireproofing (asbestos spraying)
- Asbestos textile
- Shipbuilding

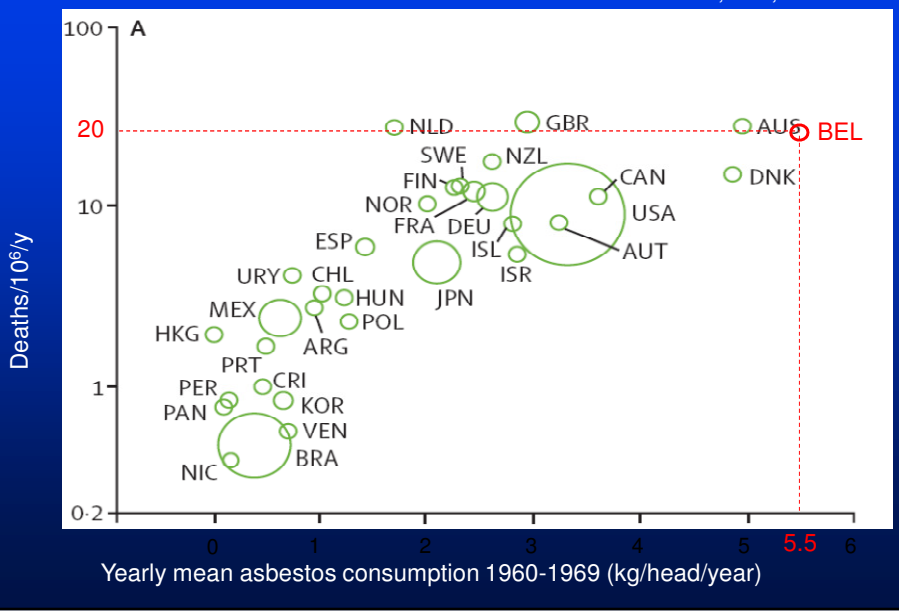
- … and more than 3000 applications



http://worldasbestosreport.org/banjan07/banjan20.pdf

Yearly mean mesothelioma deaths 2000-2004

Nawrot er al. *Lancet* 2007, 369, 1692



Asbestos exposure

- **Occupational : salaried or self-standing workers**
- **Para-occupational : households of asbestos workers (wives, children)**
- **Environmental**
  - **Naturally occurring asbestos (Turkey, Corsica …)**
  - **Neighborhood of asbestos mines or factories**
  - **Mixed environmental and para-occupational**

Evolution of occupational exposure

- Shift from traditional occupations handling raw asbestos to end-users, especially in the construction industry
- Most currently exposed workers are in contact with asbestos material still in place: heating workers, electricians, plumbers, demolition workers, asbestos removers...
- These workers are often self-standing workers or even undeclared workers

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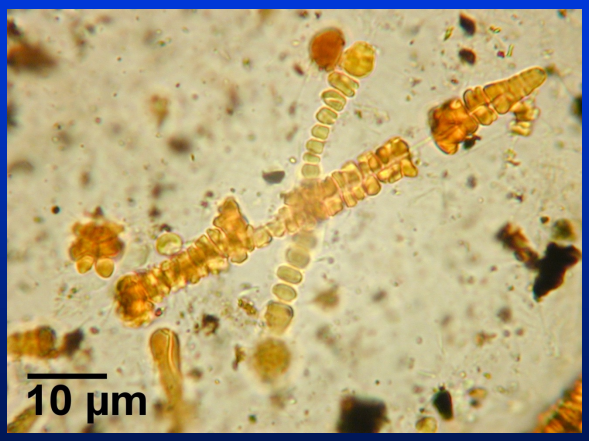
Optical microscopy

- Samples: Lung tissue, BAL
- Markers: Asbestos bodies (AB) and fibers



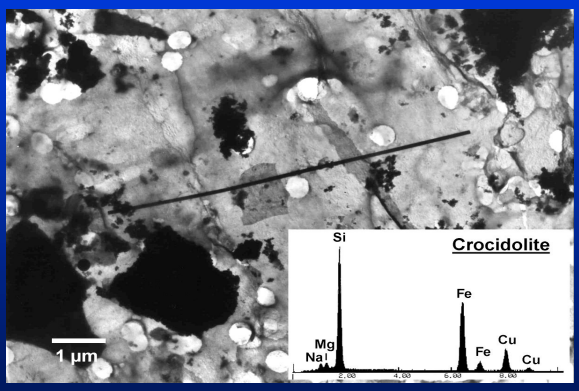
Reference values (non exposed population)

- Less than 1 AB/ml BALF (OM)
- Less than 1000 AB/g dry lung tissue (OM)
- Less than $1x10^6$ amphibole fibers/g dry lung (ELM)

De Vuyst P et al, Eur Resp J 1998;11: 1416 -1426 ERS Guidelines (Task Force)

Analytical electron microscopy

- Samples: Lung tissue, BAL
- Markers: Asbestos fibers and types of fibers
- High resolution : access to small fibers and identification



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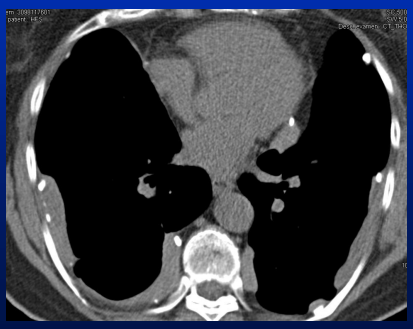
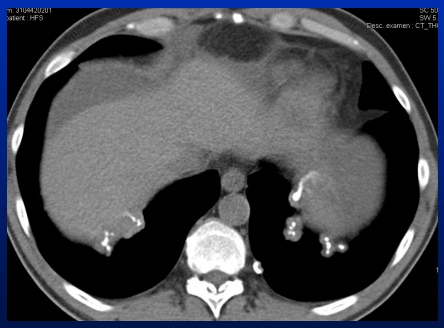
Para occupational exposure

Mr O, born in 1940. Asbestos sprayer 1963-1970. Death from mesothelioma in 2003

- **Mrs O, wife, born in 1942. Used to clean clothes and work bag each week**



- **Mr O, son born in 1968. Played with father's clothes**



Asbestos exposure

- **Occupational : salaried or self-standing workers**
- **Para-occupational : households of asbestos workers (wives, children)**
- **Environmental**
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  - **Neighbourhood of asbestos mines or factories**
  - **Indoor passive exposure in buildings**
  - **Mixed environmental and para-occupational**

Asbestos exposure

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Respiratory disorders induced by asbestos

- Asbestosis (lung fibrosis)

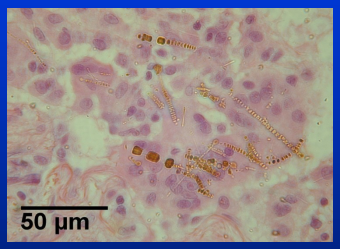
- Non-malignant pleural diseases
  - pleural plaques
  - diffuse pleural thickening (DPT)
  - benign asbestos pleural effusion

- Malignant mesothelioma
- Lung cancer

Asbestosis

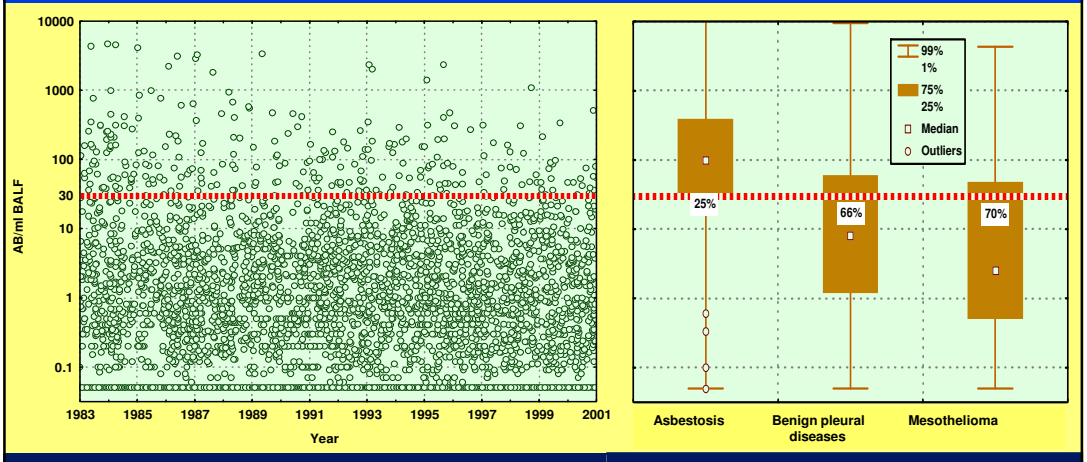
- Lung fibrosis due to substantial asbestos exposure
- Asbestosis is a « disappearing » disease in Europe

- Pathology: fibrosis with asbestos bodies in sections



- No pathognomonic clinical signs, CXR, CT (« UIP »)
- Restrictive defect with low TLCO and TLCO/VA
- Not necessarily associated with pleural lesions

AB in BAL and diseases



Dumortier P et al, Eur Respir J 2003; 22: 519-524

De Vuyst P et al, Am Rev Respir Dis 1987; 136: 1219-1224

Respiratory disorders induced by asbestos

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Pleural plaques

- Most frequent manifestation of asbestos exposure : marker of exposure rather than disease
- Circumscribed areas of fibrosis of the parietal pleura, which may calcify
- Located on the thoracic wall and on the central parts of the diaphragm
- Covered with normal mesothelium, without adherences (normal lung movements)
- No detectable effect on lung volumes in individuals, unless very extensive

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Diffuse pleural thickening (DPT)

- Diffuse fibrosis involving the visceral pleura
- Can be the sequel of a benign asbestos pleural effusion (BAPE)
- The lungs are « entrapped » (parenchymal bands and rounded atelectasis are indirect signs of DPT)
- Pleural fibrosis, adherences and loss of lung volume lead to altered lung function
- Lung function often shows a restrictive defect with decreased TLCO and normal TLCO/VA (extra-pulmonary restriction)

DPT: differences with plaques

- Diffuse pleural thickening (DPT) is a real disease with symptoms and functional repercussions
- DPT, especially when unilateral, is not a specific asbestos-related disease and it may be associated with other causes: connective tissue disorders, drug-induced pleural disease, infections...

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Asbestos and mesothelioma

- Amosite and crocidolite have a higher carcinogenic potency than chrysotile: more biopersistent in the lungs
- Historical exposures involved generally a mixture of fiber types
- The mean latency is at least 40 years since first exposure → the age at onset of exposure is crucial
- A threshold of cumulative exposure below which there is no increased risk cannot be defined: low-dose exposures can cause MM

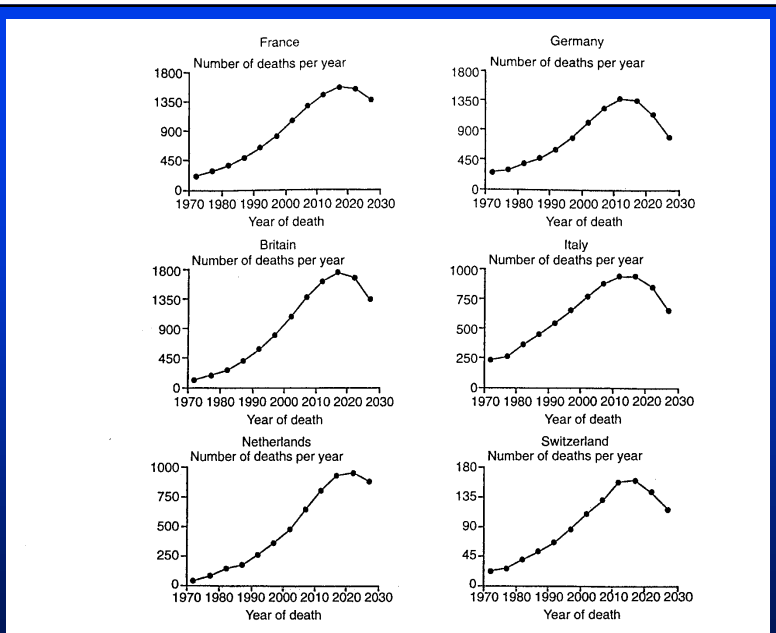


Figure 2 Observed (to 1989) and predicted (1990–2029) annual numbers of pleural cancer deaths in men in six Western European countries

The European Mesothelioma Epidemic. Peto J., et al. Br J Cancer 1999; 79 (3/4): 666-672

Gross Pathology

- INVASIVE TUMOR
- Nodules and pleural thickening
- Spreads along the surface and invades underlying structures (diaphragm, lung, pericardium…)
- Entrapment of the lung

Pathology

- **Difficult diagnosis**: panel of experts
- Two main types: epithelial (80%) and sarcomatoid (20%). Mixed types
- Immuno-histochemistry: « positive » (calretinin, mesothelin...) and « negative » markers (CEA,oestrogen receptors…)

Clinical manifestations

- Symptoms: non specific .
- Average time for diagnosis 3 months.
- Dyspnea, cough
- Chest pain (60 %)

- More than 90 % present with pleural effusion

Imaging

- Chest X Ray
  Unilateral pleural effusion
  Rarely other signs of asbestos related disease

- CT scan
  Diffuse or nodular pleural thickening
  Mediastinal involvement

  Pleural masses

Imaging

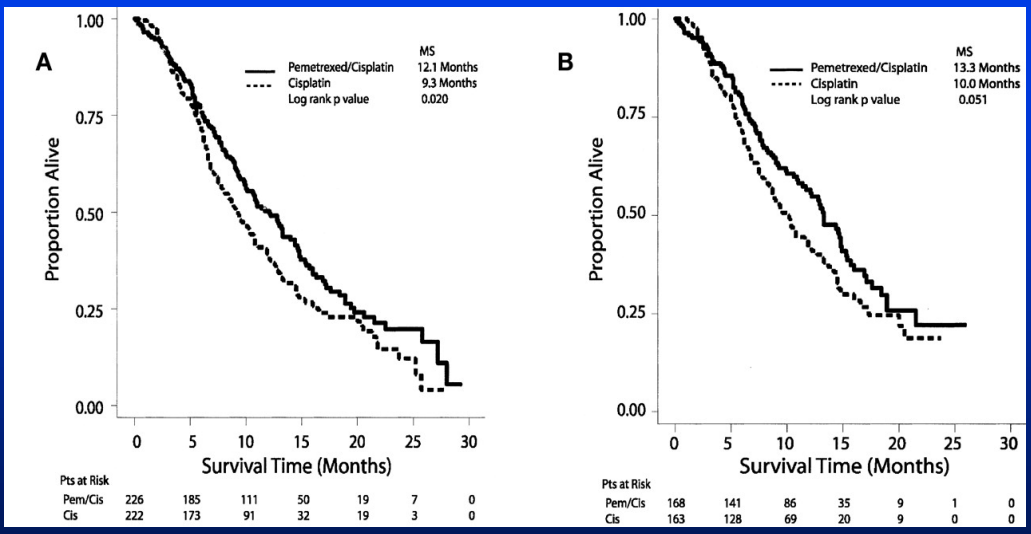
- PET/CT scan: differential diagnosis with benign asbestos related pleural effusion/ diffuse pleural thickening and for staging of MM
- MRI useful for evaluation of diaphragm and chest wall invasion (preoperative staging)

Diagnostic procedures: « tissue is the issue »

- Role of thoracoscopy for diagnosis, staging and local treatment (talc pleurodesis)

Method	No/total	%
Fluid cytology	49/175	28%
Percutaneous biopsy	33/135	24 %
Thoracoscopy	185/188	98 %
Surgery	9/9	100 %

Boutin C, et al. Cancer 1993; 72: 389-93



Vogelzang, N. J. et al. J Clin Oncol; 21:2636-2644 2003
Tableau 2 limité aux patients avec acide folique et B 12

JOURNAL OF CLINICAL ONCOLOGY

Potential utility of mesothelioma markers

Diagnosis : differentiating MPM from :

- Pleural metastases of various carcinomas
- Benign asbestos-related pleural disease
- Other pleural effusions (cardiac…)

- False positives : some adenocarcinomas (pancreas, ovary, lung, breast)
- False negatives : SMRP does not detect non-epithelial MPM

Screening among workers highly exposed to asbestos ?

Belgian study on SMRP and MPF

- Soluble Mesothelin Related Peptide
- Megakaryocyte Potentiating Factor

- « Normal » values or « cut-off » values : 2 nM/ml and 14 mg/ml (specificity 95 % and sensitivity 65 %)

Diagnostic Performance of Soluble Mesothelin and Megakaryocyte Potentiating Factor in Mesothelioma

Kevin Hollevoet[1], Kristiaan Nackaerts[2], Joël Thimpont[3], Paul Germonpré[4], Lionel Bosquée[5], Paul De Vuyst[6], Catherine Legrand[7], Eliane Kellen[2], Yoshiro Kishi[8], Joris R. Delanghe[9], and Jan P. van Meerbeeck[1]

Am J Respir Crit Care Med Vol 181. pp 620–625, 2010
DOI: 10.1164/rccm.200907-1020OC

Screening?

- Low dose CT has not been proven to be an effective screening tool for the detection of (early) MPM

- PET and MRI are not available and/or applicable for screening purposes

- No evidence that early discovery of MPM will cure the patient or even improve his survival

Eur Respir J 2010; 35: 479–495
DOI: 10.1183/09031936.00063109

ERS/ESTS TASK FORCE

Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma

A. Scherpereel, P. Astoul, P. Baas, T. Berghmans, H. Clayson, P. de Vuyst, H. Dienemann, F. Galateau-Salle, C. Hennequin, G. Hillerdal, C. Le Péchoux, L. Mutti, J-C. Pairon, R. Stahel, P. van Houtte, J. van Meerbeeck, D. Waller and W. Weder

Screening

- **A screening is justified if the early detection of the disease improves the prognosis by more effective medical or surgical treatment and if there are performant screening methods**
- **To date, according to the prevalence, prognosis, available treatments of MPM and to the performance of potential screening methods, the medical efficacy of a large-scale screening is not established**

Simulation of screening (France)

- Mesothelin: Se 80% and Sp 95%
- Incidence of MPM: 100 per million (all) exposed subjects
- Target population 6 million exposed workers

- → 600 expected MPM
- True positive cases 480 (600 x 0.8)
- False negative cases 120 (600 x 0.2)
- False positive cases 300000 (6.10 6 x 0.05)

- If test positive: less than 2/1000 « chances » to have mesothelioma

(Courtesy of Bruno Housset)

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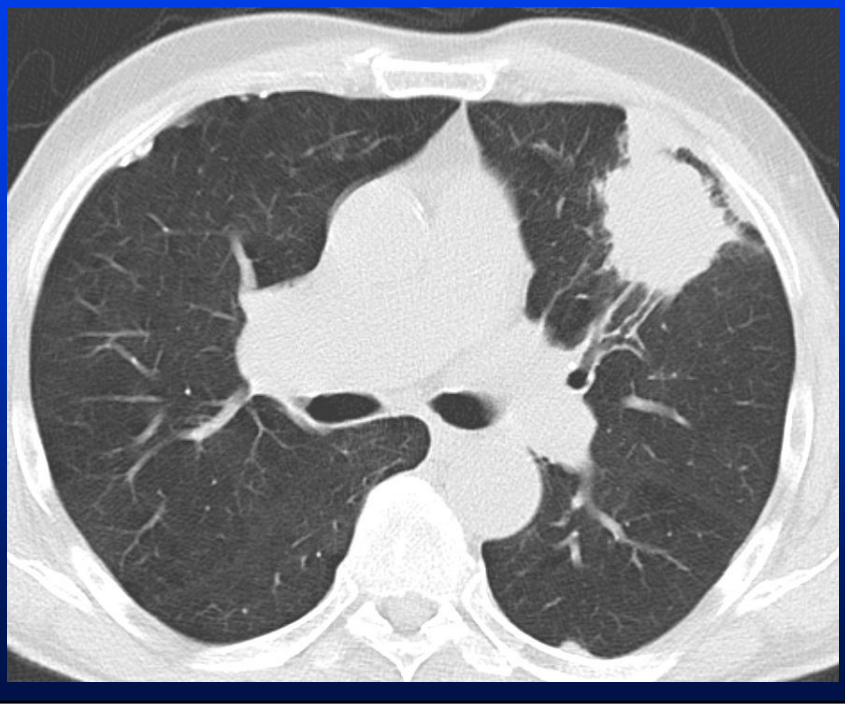
Lung cancer

- The incidence of lung cancer is increased among cohorts of asbestos-exposed workers
- All types and locations.
- Multiplicative risk with smoking
- Very difficult (impossible) to ascribe the role of asbestos in an individual case for this non-specific and frequent disease
- Association with asbestosis : still matter of debate



AB counts in tissue of lung cancer patients

	Concentration (AB/g dry LT)			
	<1000	1000-4999	5000-9999	≥ 10000
N = 1053	921	89	20	23
%	87.5 %	8.5 %	1.9 %	2.2 %

4.1 %

Overall percentage of positive cases among men : 4.9 %

P Dumortier, en préparation

Asbestos Trade Data (2006)

Top Five Producers (tons):

Russia	925,000
Kazakhstan	355,000
China	350,000
Canada	243,500
Brazil	236,100

Top Five Consumers (tons):

China	531,190
Russia	292,541
India	272,856
Kazakhstan	151,231
Brazil	143,123

Source: USGS

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Occupational Diseases Fund (ODF)

- Public organization under the authority of the Federal Ministry of Social Affairs
- Responsible for the compensation and the prevention of occupational diseases in the Belgian social welfare system
- Contributes also in reimbursement of health care costs, funeral costs or help of a third person
- Financed by employers' contributions and federal subsidiations

Requirements for recognition (ODF)

- Occupational exposure risk confirmed by an occupational enquiry (occupational engineers)
- Only for wage-earners (salaried workers). No compensation for self-employed (independent) workers

Diseases recognized in the "new system"
MB : 16/04/1999

- 130121 : Asbestosis
- 930120 : Benign pleural (and pericardial) disorders caused by asbestos
- 9307 : Mesothelioma caused by asbestos
- 9308 : Lung cancer caused by asbestos

930120 : Benign pleural disorders

- Pleural plaques
  - Usually no compensation
  - Compensation if restrictive defect related to extensive plaques (exceptional)
- Bilateral diffuse pleural thickening
  - Compensation according to the restrictive defect (cf asbestosis)
- Benign asbestos pleural effusion

Impairment directly related to reduction of lung function

Impairment (%)	1-20	21-40	41-60	61-80	81-100
FEV_1 %	84-65	64-50	49-40	39-30	< 30
VC %	84-75	74-65	64-55	54-50	< 50
TLCO %	74-60		59-50	49-40	< 40

9307 : Mesothelioma

- Diagnosis based on histopathology-immunochemistry and confirmed by experts (panel of pathologists of the “Mesothelioma Commission”)
- Recognition with "any" occupational exposure (no threshold)
- Compensation :100% impairment
- Help of a third person, reimbursement of health costs

The Belgian Asbestos Fund (AFA)

- Political decision under “social pressure” (cf France, ANDEVA and FIVA)
- ABEVA (Association belge des victimes de l’amiante)
- Legal actions for ”unforgivable fault”
- Cases of mesothelioma and neighbourhood or para-occupational exposures
- The Asbestos Fund
  - Act of December 27th, 2006
  - Effective creation on April 1st, 2007
- Organized within the ODF (FMP/FBZ)

The asbestos fund

- Everybody can apply to AFA
- Victims (and relatives) who accept the compensation by the AFA are not allowed to take further legal actions (compensation from liable third party / tiers responsable / aansprakelijke derde)
- Compensation only for mesothelioma, asbestosis and bilateral diffuse pleural thickening !
- One condition : asbestos exposure on the belgian territory only