"Global Asbestos Congress - Past, Present and Future"

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Case study (1)
The Berlaymont building.
Are there measurable health effects associated with work in a building containing flocked asbestos?

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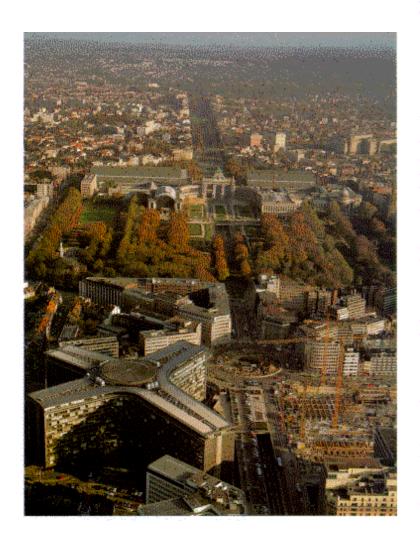
K.U.Leuven Belgium

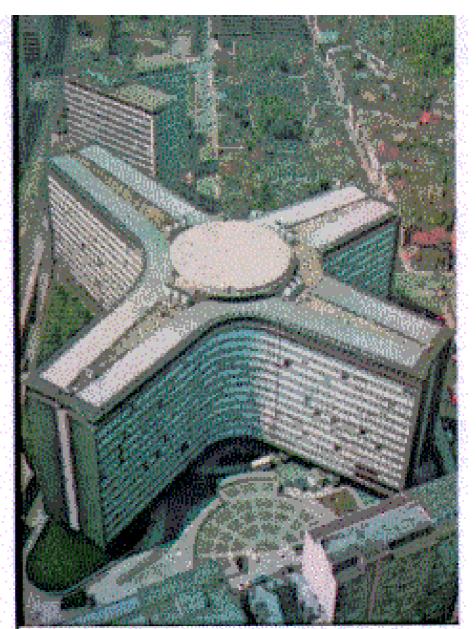
Berlaymont study

- Background
- Implementation
 - pilot phase
 - other studies
- Implications

Background

- Berlaymont building in Brussels
 - administrative headquarters of European Commission
 - start building in 1965, partly occupied from 9/1967,
 building completed in 1969: ~ 3,000 personnel
 - flocked asbestos on steel and concrete
 - numerous "incidents" with dust contamination in offices (pulling cables, renovations, ...)
 - concern among personnel & authorities
 - evacuation of building in 1991
 - asbestos removal 1995 1999, renovation 1999 -







Berlaymont study

- "Association des Victimes de l'Amiante des Communautés Européennes"
 - concern about health effects of asbestos exposure
 - claims for alleged asbestos-related disease
- Problems:
 - no serious evaluation of problem by EC authorities
 - little or no information about degree of exposure
 - limited scientific data on effects of such indoor exposure to asbestos

Berlaymont study

Proposal:

- pilot epidemiological study of possible health effects
- use sensitive technique to assess subclinical effects
- use endpoints specific for asbestos-related effects
- maximize chances of finding effects
- ethical concerns
- costs

- **Ethics**

- Sensitive technique -> Computed tomography (spiral CT + HRCT)
- ◆ Specific endpoints → Pleural lesions (plaques)
 - Maximize detection -> At least 10 y after start exposure
 - → Volunteers
 - Free choice of hospital
 - Independent researchers
 - Institutional ethics committee
 - Completely covered by EC medical service

Costs

- Pragmatic decisions:
- recruit subjects having worked ≥10 y in building for
 - questionnaire
 - clinical examination
 - pulmonary function
 - chest imaging
- analyse data from first 100 subjects
 - 2-4 subjects per week (10/1995 7/1996)

- Recruitment of subjects:
 - publicize study by various channels to reach current and retired employees
 - request forms to be obtained from EC medical service
 - possibility to be examined in various hospitals in Brussels + UZ Gasthuisberg, Leuven
- Informed consent
- Results sent to EC medical service and physician of choice

- Questionnaire (Dutch, French, English; 2 physicians)
 - administrative data
 - medical history
 - » bronchopulmonary & pleural disease (pleurisy & tb)
 - respiratory symptoms
 - smoking habits
 - occupational & environmental history
 - » duration and type of work in Berlaymont building
 - » other potential exposure to asbestos (jobs, family, hobby)
- Clinical examination: auscultation of chest

- Pulmonary function testing
 - spirometry: VC, FEV₁
 & flow-volume curve: PEF, MEF₅₀, MEF₂₅
 - body plethysmography: RV, TLC; Raw, sGaw
 - single breath diffusing capacity (transfer factor):
 DLco, Kco

predicted values (age, height) according to Quanjer et al.

- Chest imaging
 - chest x-ray (P-A & lateral)
 - CT scan
 - » no injection of contrast material
 - » spiral CT (1 cm thick)
 - » High Resolution CT (1 mm thick, every 1 cm)
 - » supine position + some images in prone position
 - all scans were read by one experienced radiologist, aware of origin of subject ("Berlaymont protocol"), but unaware of past clinical or occupational history

Imaging of asbestos-induced lesions

Lung tissue

- interstitial lung disease (asbestosis)
- rounded atelectasis
- bronchopulmonary cancer

Pleura

- pleural effusion
- diffuse pleural thickening
- pleural plaques
- malignant mesothelioma

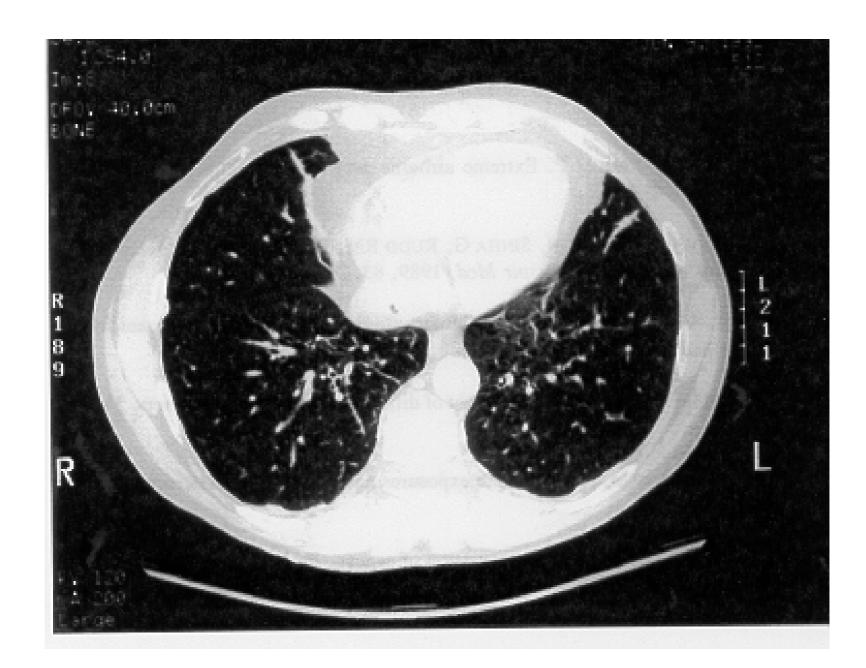
Asbestos-induced lesions

Past exposure Specificity

| asbestosis | +++ | + |
|------------------------------------------------|-----|-----|
| bronchopulmonary cancer | ++? | _ |
| pleural effusion | ++ | _ |
| diffuse pleural thickening | ++ | -/+ |
| rounded atelectasis | ++ | + |
| pleural plaques | + | +++ |
| malignant mesothelioma | + | +++ |

Pleural plaques

- focal (localized, circumscribed) thickening of the parietal pleura
- acellular (hyaline), may become calcified
- poor relation with asbestosis
- no symptoms
- mostly postero-lateral & diaphragm (pericard)
- usually bilateral
- pathognomonic for past asbestos exposure



| | total | female | male |
|-------------------|---------------|---------------|---------------|
| number | 100 | 55 | 45 |
| age (y) | 55 | 54 | 56 |
| range | 40 -77 | 44 - 68 | 40 - 77 |
| in Berlaymont (y) | 17 10 - 24 | 17 10 - 22 | 17 10 - 24 |
| smoking NS | 40 % | 44 % | 36 % |
| XS | 45 % | 46 % | 44 % |
| S | 15 % | 11 % | 20 % |

| | | total | female | male |
|-----|------------------------|-------|--------|------|
| nun | nber | 100 | 55 | 45 |
| job | administrative1 | 73 % | 84 % | 60 % |
| | "other" ² | 22 % | 16 % | 29 % |
| | technical ³ | 5 % | 0 % | 11 % |

¹ pure office work

² courier-receptionist, archives, library, ...

³ electricity, air conditioning, maintenance

- Pulmonary function tests
 - no pathological values
 - » except known disease (smoking, asthma)
 - no significant differences between job categories

Chest x-ray and CT

- no cases of pulmonary fibrosis, diffuse pleural thickening, lung cancer or mesothelioma
- incidental findings in some: emphysema, sequelae of infections, extra-pulmonary lesions or abnormalities
- -pleural abnormalities in 13 subjects
 - » generally discrete
 - » "compatible with pleural plaque, as caused by asbestos exposure" (alternative possibilities also evoked in some)

Pleural abnormalities on (HR)CT

Radiologist: "compatible with asbestos plaques"

| | females | males |
|------------|---------|-----------------------|
| n | 55 | <i>4</i> 5 |
| bilateral | 1 a | 8 ^{a,b} |
| unilateral | 0 | 4 ^b |

^a 1 subject with history of tuberculosis

^b 1 subject with history of pleurisy in youth

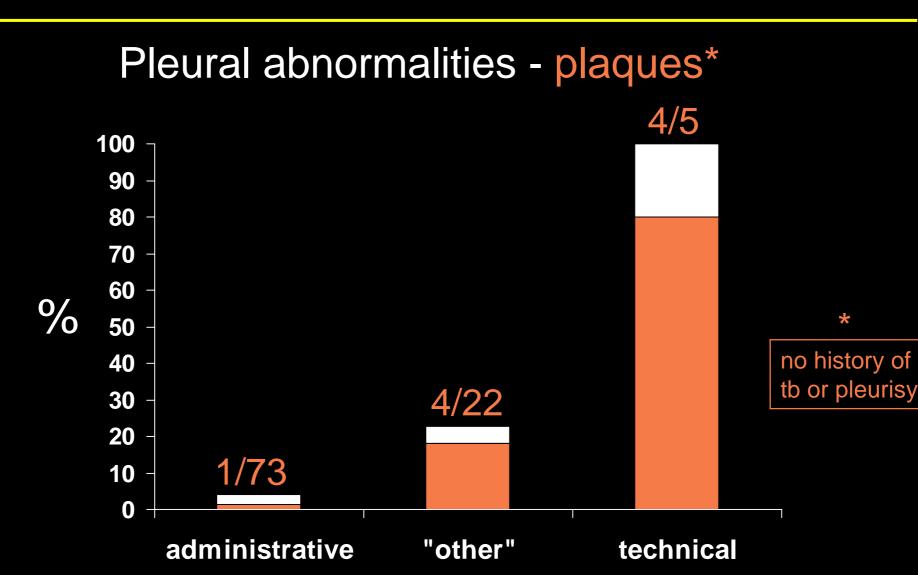
Pleural abnormalities on (HR)CT

Radiologist: "compatible with asbestos plaques"

| | administrative "other" | | technical |
|--------|------------------------|--------------------|-------------------|
| n | 73 | 22 | 5 |
| female | 1ª/46 | 0/9 | 0/0 |
| male | 2ª/27 | 5 ^b /13 | 5 ^b /5 |

^a 1 subject with history of tuberculosis

b 1 subject with history of pleurisy in youth



- Pleural abnormalities / plaques
 - positive relation with (presumed) exposure intensity
 - no relation with smoking
 - inconclusive relation with duration of employment in Berlaymont:
 - » subjects with pleural abnormalities: 20.2 y
 - » subjects without pl. abnormalities: 16.5 y (p < 0.05, but probably confounded by technicians having been employed longer)</p>
 - no differences in pulmonary function

Berlaymont pilot study - summary

- No "serious" asbestos-related disease detected
- (Small) pleural plaques were found in 13 subjects
 - 80 % of employees who had direct occupational contact with asbestos (technicians)
 - 18 % of employees ("others") who had no direct contact with asbestos, but presumably a higher "passive" exposure than administrative jobs (~1%)
 - = (unplanned) validation of the sensitivity of the technique and of the quality of our radiologist, who was unaware of the job categories

Berlaymont pilot study - problems

Representative population - recruitment bias?

- overrepresentation of technicians and "others", but exact size of target population and distribution of jobs is unknown!
- within each category, volunteers were probably the most health-conscious or worried subjects, but this should not constitute a significant bias
 - » plaques do not cause symptoms
 - » unlikely to be related to intensity of past asbestos exposure
- most volunteers (still) lived in Belgium; unlikely to be significant
- findings in employees studied elsewhere (>400) are (still) largely unknown

Berlaymont pilot study - problems

- Identification of subtle pleural lesions as "plaques"
 - over-diagnosis ? (fat, muscle, lymph nodes, ...)
 - under-diagnosis ?

Study intra-reader and inter-reader variability in detecting and interpreting subtle pleural lesions

Methods (1)

- 100 spiral and HRCT scans were read again independently by three radiologists (A, B, C)
 - » A = academic chest radiologist: initial reading (A1) and repeated reading (A2) at least 6 months later
 - » B = academic chest radiologist from other university, specialised in compensation problems
 - » C = general radiologist
 - all unaware of initial diagnosis and exposure category

Methods (2)

- scans scored re. pleural changes on a 5-point scale
 - » 0 = normal (incl. subcostal fat, intercostal muscles, vessels)
 - » 1 = abnormal, but not pleural plaque (e.g. sequelae of tb or pleurisy, subpleural nodule)
 - » 2 = abnormal with low probability of plaque
 - » 3 = abnormal with moderate probability of plaque
 - » 4 = abnormal with high probability of plaque

based on presence, extent, distribution and appearance of the changes and correspondence with literature and personal experience

- Methods (3)
 - for all scans with pleural abnormality identified at least once: consensus reading session with all three readers

Results (1)

| score | A1 | A2 | В | С | consensus |
|-----------------------|----|----|----|----|-----------|
| 0 (normal) | 87 | 80 | 88 | 75 | 82* |
| 1 (not pleural pl.) | 4 | 8 | 7 | 19 | 7 |
| 2 (low prob. pl.pl.) | | 1 | 3 | 6 | 2 |
| 3 (medium prob.) | 9 | 5 | 0 | 0 | 4 |
| 4 (high prob. pl.pl.) | | 6 | 2 | 0 | 5 |

* 64 [000]; 16 [00]; 2 [0]

8 [+++]; 5 [++]; 4 [+]; 1 [0]

Results (2): 6 statistics

intra-observer agreement: 6

A1 vs A2 0.68 good

– inter-observer agreement: weighted 6

A2 vs B 0.43 moderate

A2 vs C 0.45 moderate

B vs C 0.26 fair

Conclusions

- detection and interpretation of discrete pleural abnormalities by CT scanning is subject to considerable observer variation
- strict methodological precautions need to be taken in epidemiological studies (multiple readers, blinded)
- the conclusions of the pilot study were not invalidated

Berlaymont pilot study - problems

- What is the background prevalence of such small (asbestos) plaques in the population?
 - little or no literature on prevalence of pleural plaques (by CT) in non-industrial populations

Examine suitable control population using methods with similar sensitivity

Investigation of control subjects

- 100 male and female "white collars" > 45 y without known exposure to asbestos & without history of tb or pleurisy, volunteers recruited from
 - personnel of EC without work in Berlaymont building
 - personnel from university and hospital
 - relatives and friends
- all methods similar as for Berlaymont subjects, except no spiral CT (radiation hazard)
- funded by EC

Investigation of control subjects

- all methods similar as for Berlaymont subjects, except no spiral CT (radiation hazard)
- all HRCT scans read by same three radiologists
 - scans from control and exposed subjects mixed and dates erased
 - independent scoring followed by consensus reading

! preliminary results only

Berlaymont vs controls - results

| | Berlaymont | controls |
|------------------|----------------------|----------------------|
| number | 130* | 100 |
| male/female | 54%/46% | 49%/51% |
| age (y) range | 54 34 - 76 | 56 45 - 76 |
| smoking NS | 39% | 47% |
| XS | 42% | 29% |
| S | 19% | 22% |

^{*} only "white collars" (7 technicians excluded)

Berlaymont vs controls - results

- Pulmonary function tests
 - no significant differences in any parameter

Berlaymont vs controls - results

Pleural abnormalities by HRCT

| | Berlaymont | controls |
|---------|------------|----------|
| number | 130* | 100 |
| score 1 | 14 (10.8%) | 9 (9%) |
| 2 | 7 (5.4%) | 1 (1%) |
| 3 | 2 (1.5%) | 3 (3%) |
| 4 | 0 (0%) | 1 (1%) |
| 2+3+4 | 9 (6.9%) | 5 (5%) |

Berlaymont vs controls - discussion

- 5 control subjects with pleural plaques!
 - 1 with possible environmental exposure (Greece)
 - 2 with possible indoor asbestos exposure in (university) building
 - 2 with possible occupational exposure (salesman, engineer)
 - no such histories in most other control subjects (to be checked independently)
- difficult to define "perfect" control group!

Other approach to assess background prevalence of pleural plaques

- In 117 successive thoracotomy patients > 45 y:
 - visual inspection of hemithorax for presence of "plaques" by surgeon + fill out standard form
 - detailed occupational and environmental history
 - manual/technical job with definite/possible contact with asbestos:
 - unlikely occupational contact with asbestos: 1/15

 - ~ 6% prevalence in subjects without direct exposure

Berlaymont study - problems

- What is the (cumulative) exposure to asbestos?
 - were the "other" employees really exposed more ?
- Evaluate all available dust measurements
 - > 5000 measurements of asbestos (optical) made 1971-1991
 - -6 samples > 0.2 f/ml (0.3-3.9 f/ml)
 - these hygiene data have not (yet) been made available to perform an analysis by area, time, fibre type ...
- Count asbestos bodies in BAL (or sputum?)
 - few subjects have undergone bronchoscopy + BAL (ethics ?)

Berlaymont study - implications

- Significance of finding (small) pleural plaques?
 - for the individual
 - » evidence of (excessive) exposure to asbestos
 - » no influence on ventilatory function, no physical impairment
 - » as such, probably (?) no influence on life expectancy (plaques are <u>not</u> premalignant lesions)
 - » moral prejudice anxiety (individual, relatives)
 - for the group
 - » evidence of excessive exposure to asbestos
 - » increased risk of malignant tumours
 - » anxiety

Berlaymont study - implications

- Which advice and follow-up?
 - Individual subjects with pleural abnormalities
 - » which method? Chest x-ray or HRCT? Lung function?
 - » how frequently? Every 1, 3 or 5 years?
 - » which objective? Reassurance? Progression of benign lesions? Detection of malignant lesions? "Cost"/Benefit?
 - » smoking cessation
 - Individual subjects without abnormalities
 - » same considerations
 - Group: collect epidemiological information

The Berlaymont study

Are there measurable health effects associated with work in a building containing flocked asbestos?

- Technicians: yes
- Purely administrative work: no evidence, so far
- "Others": probable, but not proven
- despite many favourable conditions (large study group, few financial constraints), the scientific evidence is difficult to obtain
- poor documentation of level of exposure
- hard to find truly unexposed population for comparison
- further longitudinal follow-up needed

The Berlaymont study

- The study has numerous implications which are not always easy to manage
 - scientific uncertainty
 - risk communication
 - delicate balance between reassuring individuals and not being complacent with public health hazards
 - which follow-up is most appropriate?

– ...



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