Occupational Exposure Assessment:

We can make it more interesting, but not easier!

Hans Kromhout
Background

- Need for quantitative exposure assessment for epidemiology is becoming the norm rather than the exception.
- Risk assessors need and want quantitative exposure response relations.
- Regulators and exposed individuals want to know whether a certain level is safe or not.
- With increasing information on individual susceptibility, more detail will be needed in exposure assessment and assignment (end of the group-based approach?)
Lay-out

- Back to the basics: exposure assessment and exposure assignment in occupational epidemiology
- Some early examples
- Industrial versus general population studies
- Current day opportunities
- Looking into the future
Exposure Assessment

Environments can be quite different

Institute for Risk Assessment Sciences
Exposure Assessment

Oncology nurses

Potential dermal exposure to the hands

Exposures might not occur in a simple manner

Institute for Risk Assessment Sciences
Exposure Assignment

- Linking the individual subject to an exposure measure via his/her job history

- In occupational studies on chronic health effects this is mainly done at group level

- Exposure might have been collected for some of study subjects in the past but not for all and definitely not for all relevant time periods

Only for (panel) studies or cross-sectional studies looking at acute effects exposure might be assessed and assigned at individual level
Early examples

  - Detailed records of plant processes and dust control methods over the period 1930-1975 were collected
  - Developed linear statistical models to reconstruct historical exposures
  - Parameters were estimated using 5,952 industrial hygiene sampling measurements collected in the same period!
  - Extrapolation was actually minimal, except that all measurements were done stationary i.e. o. personally
    They had to deal with changes in measurement methods over time
Early examples


- Exposure data: 6395 records covering 1948-1988
- Conversion factors
- 0.37 mg/m$^3$ in 50-ies 0.17 later
- Considerable amount of extrapolation needed

Institute for Risk Assessment Sciences
Are we critical enough in evaluating epi-evidence

- A lot of guessing and extrapolation is going on, but are we actually aware of this?
- Let’s have a look at a couple of very important epi-studies on benzene and leukemia

Work history years density plot
Australian benzene study

Work history years density plot
Canadian benzene cohort
Is there any measurement data around in the first place?

The EXASRUB Project

Institute for Risk Assessment Sciences
Power of industry-wide databases
Improved Exposure Assessment for Prospective Cohort Studies and Exposure Control in the Rubber Manufacturing Industry
Power of industry-wide databases: ExAsRub

• EU funded Concerted Action
• started January 2002 ended June 2004
• Within 2 months 27,000 measurements were identified and access to the data ascertained

• ExAsRub DBMS was elaborated
• All data transferred into the database by the end of 2002
The EXASRUB interface: Data Entry

Institute for Risk Assessment Sciences
Power of industry-wide databases
Measurements and samples by country

N = 59.609
N(ind) = 27.095

Individual Measurements
Independent samples

Institute for Risk Assessment Sciences
Power of industry-wide databases
main agents

\[ N_{\text{dust}} = 13.655 \]
\[ N_{\text{nitrosamines}} = 21.202 \]
\[ N_{\text{fumes}} = 5.932 \]
\[ N_{\text{solvents}} = 5.932 \]
Power of industry-wide databases

Crude Materials, Compounding and Mixing

Time trend per year

UK : -6%
NL : -2%
PL : -6%
SW : -6%
GE : -7%
Power of industry-wide databases
EXASRUB: other findings

- Exposure measurements available for each year between 1965 and 2002
- Surveys were predominantly done either as routine surveys or to test compliance
- A wide range in sampling strategies and sampling/analytical methods present
Will it be used at all?

- Uncertain, but we are ready to do the exposure assessment in a standardized quantitative way
- The approach is currently being used to study an update of cancer mortality in the Polish rubber manufacturing industry
- The icing on the cake will be to show that it also works in a European wide pooled cohort study
- But given the macroeconomic developments in this industry the epi-study eventually will have to be carried out in India or China
So it can be done in industry-based studies!

- But what about general-population based studies?

- For instance will we be able “to go quantitative” in hospital-based case-control studies where we are dealing with a multitude of industries, jobs and workplaces.
Will collecting quantitative data solve the basic problem

- It’s unlikely, but worth a try

- The SYNERGY Study
  - Pooling major lung cancer case control studies
  - In order to get an idea of interaction between concurrent exposure to more than one lung carcinogen and smoking
  - Focus is on 5 major lung carcinogens: asbestos, silica, PAHs, nickel and chromium
  - Trying to build an industry (ISICa) - job (ISCOb) - country - time period measurement data-based exposure matrix
  - To do so we are harvesting existing measurement databases
Synergy pooling the major recent lung cancer case-control studies
Status by sex and study

<table>
<thead>
<tr>
<th>Status</th>
<th>Men</th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>AUT</td>
<td>2659</td>
<td>49.6</td>
<td>2702</td>
<td>50.4</td>
</tr>
<tr>
<td>EAGLE</td>
<td>1538</td>
<td>48.7</td>
<td>1617</td>
<td>51.3</td>
</tr>
<tr>
<td>HdA</td>
<td>839</td>
<td>50.0</td>
<td>839</td>
<td>50.0</td>
</tr>
<tr>
<td>INCO</td>
<td>2057</td>
<td>50.5</td>
<td>2013</td>
<td>49.5</td>
</tr>
<tr>
<td>INCO_UK</td>
<td>281</td>
<td>32.9</td>
<td>574</td>
<td>67.1</td>
</tr>
<tr>
<td>LUCA</td>
<td>310</td>
<td>50.7</td>
<td>302</td>
<td>49.3</td>
</tr>
<tr>
<td>LUCAS</td>
<td>1042</td>
<td>30.6</td>
<td>2364</td>
<td>69.4</td>
</tr>
<tr>
<td>PARIS</td>
<td>161</td>
<td>42.4</td>
<td>219</td>
<td>57.6</td>
</tr>
<tr>
<td>ROME</td>
<td>296</td>
<td>52.7</td>
<td>266</td>
<td>47.3</td>
</tr>
<tr>
<td>TURIN</td>
<td>956</td>
<td>43.3</td>
<td>1253</td>
<td>56.7</td>
</tr>
<tr>
<td>TOTAL</td>
<td>10139</td>
<td>45.5</td>
<td>12149</td>
<td>54.5</td>
</tr>
</tbody>
</table>
Mean job periods by sex and study

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (min – max)</td>
<td>Mean (min – max)</td>
<td>Mean (min – max)</td>
<td>Mean (min – max)</td>
</tr>
<tr>
<td>AUT</td>
<td>4.06 (1-18)</td>
<td>4.11 (1-19)</td>
<td>3.75 (1-17)</td>
<td>3.73 (1-16)</td>
</tr>
<tr>
<td>EAGLE</td>
<td>2.48 (1-14)</td>
<td>2.54 (1-13)</td>
<td>2.12 (1-10)</td>
<td>2.12 (1-10)</td>
</tr>
<tr>
<td>Hda</td>
<td>5.23 (1-31)</td>
<td>5.35 (1-24)</td>
<td>4.85 (1-18)</td>
<td>4.76 (1-20)</td>
</tr>
<tr>
<td>INCO</td>
<td>3.18 (1-21)</td>
<td>3.17 (1-15)</td>
<td>2.78 (1-13)</td>
<td>2.81 (1-13)</td>
</tr>
<tr>
<td>INCO_UK</td>
<td>4.69 (1-21)</td>
<td>5.03 (1-20)</td>
<td>4.54 (1-17)</td>
<td>4.66 (1-18)</td>
</tr>
<tr>
<td>LUCA</td>
<td>3.12 (1-11)</td>
<td>3.02 (1-12)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LUCAS</td>
<td>2.40 (1-10)</td>
<td>2.69 (1-9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PARIS</td>
<td>1.91 (1-5)</td>
<td>1.80 (1-5)</td>
<td>1.88 (1-5)</td>
<td>1.56 (1-4)</td>
</tr>
<tr>
<td>ROME</td>
<td>2.10 (1-8)</td>
<td>2.10 (1-7)</td>
<td>1.39 (1-4)</td>
<td>1.31 (1-3)</td>
</tr>
<tr>
<td>TURIN</td>
<td>3.25 (1-15)</td>
<td>3.43 (1-17)</td>
<td>2.70 (1-13)</td>
<td>2.28 (1-11)</td>
</tr>
</tbody>
</table>
What do we have?

- Measurements from existing exposure databases will be complemented with data collected by local experts.
- First inventory resulted in an estimated 73,000 personal and 188,000 stationary measurements of the selected agents available in European databases.
What do we have?

Institute for Risk Assessment Sciences
What will we get?

- A lot, but some data owners are not easily persuaded to hand over their individual measurement results together with contextual information.
- Individual data needed, because we will have to make adjustments for differences in measurement strategy, measurement devices, analytical procedures etc.
- Turns out that getting data from insurance type institutions like BGIA (MEGA database with more than 2 million measurements) and INRS (COLCHIC) is much harder than we thought.
Synergy Exposure Database

SynExDB

Over 16,000 individual data points already in requested database format

- 75% personal measurements; 25% stationary
- From ten European countries
- 1965 - 2007
Synergy Exposure Database

Lot of other data promised:

- EXPO Norway
  - ~8,500 personal
  - ~2,500 stationary
- SWEA Sweden (~1,000)
- MEGA Germany ???
  - ~35,000 personal
  - ~150,000 stationary
- COLCHIC France ???
  - ~35,000 personal
  - ~27,000 stationary
- Several Italian institutes
- Several East European institutes (Slovakia, Romania, Russia)
Overlap

Is there overlap of data points in the exposure database and job periods of Synergy subjects so far?

26,810 subjects
- 14,696 cases
- 12,114 controls

In total 123,112 jobs, representing 1,264,593 working years from 1922 until 2005
## Distribution Working Years

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Working years</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1970</td>
<td>610,582</td>
<td>48%</td>
</tr>
<tr>
<td>1970-1979</td>
<td>274,439</td>
<td>22%</td>
</tr>
<tr>
<td>1980-1989</td>
<td>244,829</td>
<td>19%</td>
</tr>
<tr>
<td>1990-1999</td>
<td>122,892</td>
<td>10%</td>
</tr>
<tr>
<td>≥2000</td>
<td>11,851</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,264,593</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

For 359 job periods the time period unknown

*Institute for Risk Assessment Sciences*
### Overlap Working Years – Data Points

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Working years</th>
<th>Number exposure data points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1970*</td>
<td>610,582</td>
<td>859</td>
</tr>
<tr>
<td>1970-1979</td>
<td>274,439</td>
<td>177</td>
</tr>
<tr>
<td>1980-1989</td>
<td>244,829</td>
<td>7,846</td>
</tr>
<tr>
<td>1990-1999</td>
<td>122,892</td>
<td>5,966</td>
</tr>
<tr>
<td>≥2000</td>
<td>11,851</td>
<td>1,506</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,264,593</strong></td>
<td><strong>16,384</strong></td>
</tr>
</tbody>
</table>

*Job periods from start from 1922; measurement data from 1965

Institute for Risk Assessment Sciences
Overlap Working Years – Data Points (by time period)

1: <1970
2: 70-79
3: 80-89
4: 90-99
5: =>2000

Institute for Risk Assessment Sciences
## Distribution Working Years

<table>
<thead>
<tr>
<th>Major ISCO groups</th>
<th>years</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/1 – Professional and technical</td>
<td>135,539</td>
<td>11%</td>
</tr>
<tr>
<td>2 – Administrative and managerial</td>
<td>42,685</td>
<td>3%</td>
</tr>
<tr>
<td>3 – Clerical</td>
<td>147,509</td>
<td>12%</td>
</tr>
<tr>
<td>4 – Sales</td>
<td>73,108</td>
<td>6%</td>
</tr>
<tr>
<td>5 – Service</td>
<td>74,999</td>
<td>6%</td>
</tr>
<tr>
<td>6 – Agricultural etc.</td>
<td>67,911</td>
<td>5%</td>
</tr>
<tr>
<td>7/8/9 – Production, transport, labourers</td>
<td>551,671</td>
<td>44%</td>
</tr>
<tr>
<td>Unknown</td>
<td>171,171</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Total</strong>*</td>
<td>1,264,593</td>
<td>100%</td>
</tr>
</tbody>
</table>
Whatever happens

- We will have to do a considerable amount of extrapolation (hardly any data from Eastern Europe) but also a lot of job history years are from before 1980-ies

- But at least it will be data-driven, verifiable and accountable (no black-box exposure assessment by experts)

- There will be enough room and opportunity for sensitivity analyses
Why are we making our live so difficult?

- Using the pooled case-control studies databases we had a quick look at the relation between exposure to diesel motor emissions and lung cancer
- Roel Vermeulen and I build a simple semi-quantitative ISCO-based Job Exposure Matrix for DME on a Friday afternoon, that was linked to the job histories:
- And see what we got:

<table>
<thead>
<tr>
<th></th>
<th># cases</th>
<th># controls</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>6975</td>
<td>9300</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>3975</td>
<td>4473</td>
<td>1.14</td>
<td>1.08-1.20</td>
</tr>
<tr>
<td>High</td>
<td>1256</td>
<td>1034</td>
<td>1.45</td>
<td>1.33-1.59</td>
</tr>
</tbody>
</table>

I guess we needed a challenge!

Institute for Risk Assessment Sciences
What about the future?
Clear need for improvement coming from molecular epidemiology arena

From Vineis at X2004 (Int J Epi 2004):
“disproportion between accuracy of environmental measurements and that of genotyping”
“genotyping not only tends to be much more accurate (sensitivity and specificity, greater than 90%) but in addition many genetic polymorphisms are far more frequent (prevalence order of 40-50%) than most exposures”
“probability of finding results for genes tends to be higher than for environmental exposures”
“this should lead us to improve our exposure assessment tools”

However, even with improved tools the nature of occupational exposure will stay erratic and not become binary (again)!

Institute for Risk Assessment Sciences
Future of exposure assessment for epidemiologic research

• Less involvement of OH/IH when they continue their quest for and application of “generic models”

• Plenty of opportunities for exposure assessors
  – Vineis 2004: “the only solution I foresee is to empower exposure assessment, by investing in strong and validated exposure assessment procedures”
  – Toraason et al. 2004: “perform quantitative exposure assessments, as qualitative exposure assessments that rely on general classification of occupation are not good enough”

• Increase application of self-assessment methods with less direct involvement of experts

_Institute for Risk Assessment Sciences_
Building an industry-wide occupational exposure database for respirable mineral dust

Experiences from the IMA Dust Monitoring Programme
History

Situation 2000 within Industrial Minerals industry:
- Hardly any exposure data on RCS
- Available exposure data not comparable (different measurement strategy, different data quality)
- Not representative for exposure within IM industry

IMA-Europe took initiative to create an exposure database

Arbo Unie & IRAS involved since 2006
Why did industry want to build an exposure measurement database?

- To have (statistically) reliable exposure data
- To be able to discuss with authorities on new/future OEL’s
- To develop prevention strategies to reduce exposure (develop prevention culture)
- To improve compliance with current OEL’s
  - On industry level
  - On company level
- To be used as a resource for exposure assessment for future epidemiological studies
Comparable and high quality data: Requirements

- Collect 6 samples per job function
  - Statistical needs
  - Practical feasibility for participating companies

- Quartz analyses: IR or XRD

- Laboratories: join an inter-laboratory round-robin exercise

- Record work activities, use ppe’s etc during sampling

- Transmission of data in standardised MS Excel® collection sheet

Institute for Risk Assessment Sciences
Status of participation
13 campaigns

24 companies (several SME’s)
85 sites

13 countries

10,207 RD observations
8,533 quartz analyses
(1,000-1,500 new samples/year)

~ 5000 workers
(2000 monitored)
Geographical distribution
Company

Sampling by:
- Company representatives
- External IH / laboratory
Company

Submit data

Arbo Unie / IRAS

- Extensive data check
- If needed communication with company representatives
Company -> Company report

Arbo Unie / IRAS

Add data

Exposure database
IMA-Europe

Company

Arbo Unie / IRAS

Exposure database

Analyses of pooled data

Yearly

Institute for Risk Assessment Sciences
Company

Feed back
- Report
- Debriefing meetings

IMA-Europe

Arbo Unie / IRAS

Institute for Risk Assessment Sciences
Company

IMA-Europe

Feed back
- Report
- Debriefing meetings

Arbo Unie / IRAS

Companies anonymous in IMA-report
Example:

Time trends visible

Geometric mean quartz exposure

<table>
<thead>
<tr>
<th>Job functions</th>
<th>Concentration (mg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QO</td>
<td>1.3</td>
</tr>
<tr>
<td>WP</td>
<td>3.0</td>
</tr>
<tr>
<td>DP</td>
<td>4.0</td>
</tr>
<tr>
<td>DP</td>
<td>4.1</td>
</tr>
<tr>
<td>BO</td>
<td>6.1</td>
</tr>
<tr>
<td>BO</td>
<td>6.3</td>
</tr>
<tr>
<td>TW</td>
<td>7.1</td>
</tr>
<tr>
<td>FM</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Example of site report
Box plots represent distribution, median and mean of observed dust concentrations. The estimated time trend in dust concentrations is based on the observed dust concentrations and corrected for influences of site and job title.

Estimated average trend per campaign = \(-13\%\)

95% CI: 11.6% - 14.5%
Silica

Estimated average trend per campaign = -13 %

Respirable dust!

95% CI: 11.6% - 14.5%

Box plots represent distribution, median and mean of observed dust concentrations. The estimated time trend in dust concentrations is based on the observed dust concentrations and corrected for influences of site and job title.
Message

- Possible to build an industry-wide occupational exposure database
  - Multi-national
  - Both large companies & SME
  - Has high quality data at reasonable costs

- Potential of this unique database is high
  - Risk management tool for individual companies
  - Risk management tool for industry sector
  - For future evaluation of health effects due to exposure to respirable crystalline silica
Conclusions

- Quantitative exposure assessment for epidemiology is possible
- Whether it can be done outside industry-based studies is questionable and still has to be proven (Synergy study)
- We should start making use of measurement data collected in the 1980-2000 to give more weight to epi-evidence
- It might be the only slot in history where we can actually do it given the lack of interest in collecting measurement data in present days
- Luckily there are exceptions and consequently opportunities around at the same time (IMA dust monitoring database)