Universiteit Utrecht

Occupational Exposure Assessment:

We can make it more interesting, but not easier!

Hans Kromhout

Institute for Risk Assessment Sciences

Background

- Need for quantitative exposure assessment for epidemiology is become 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

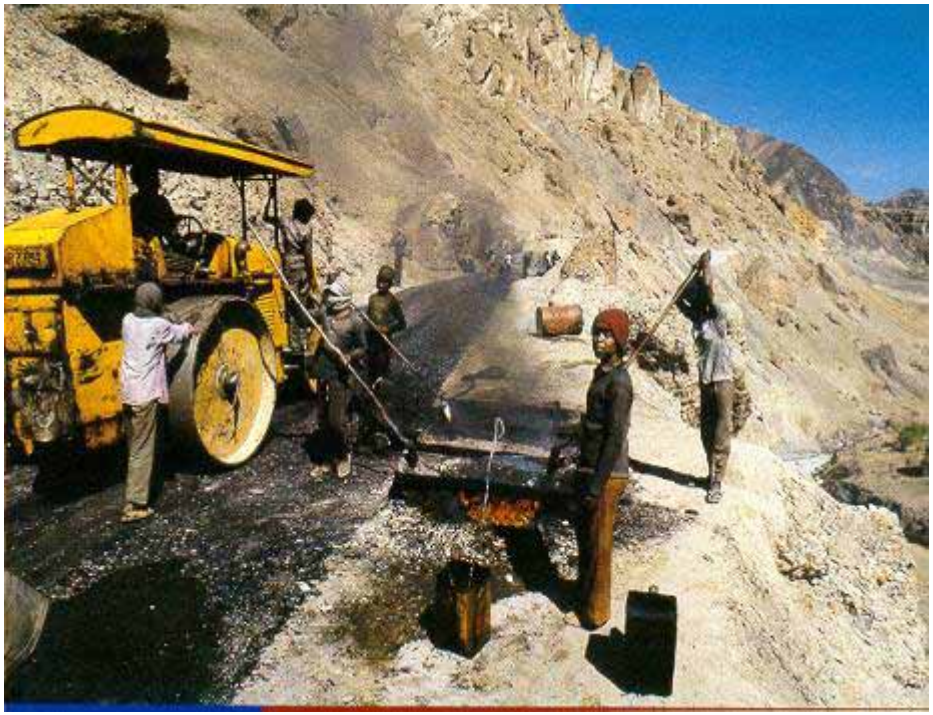
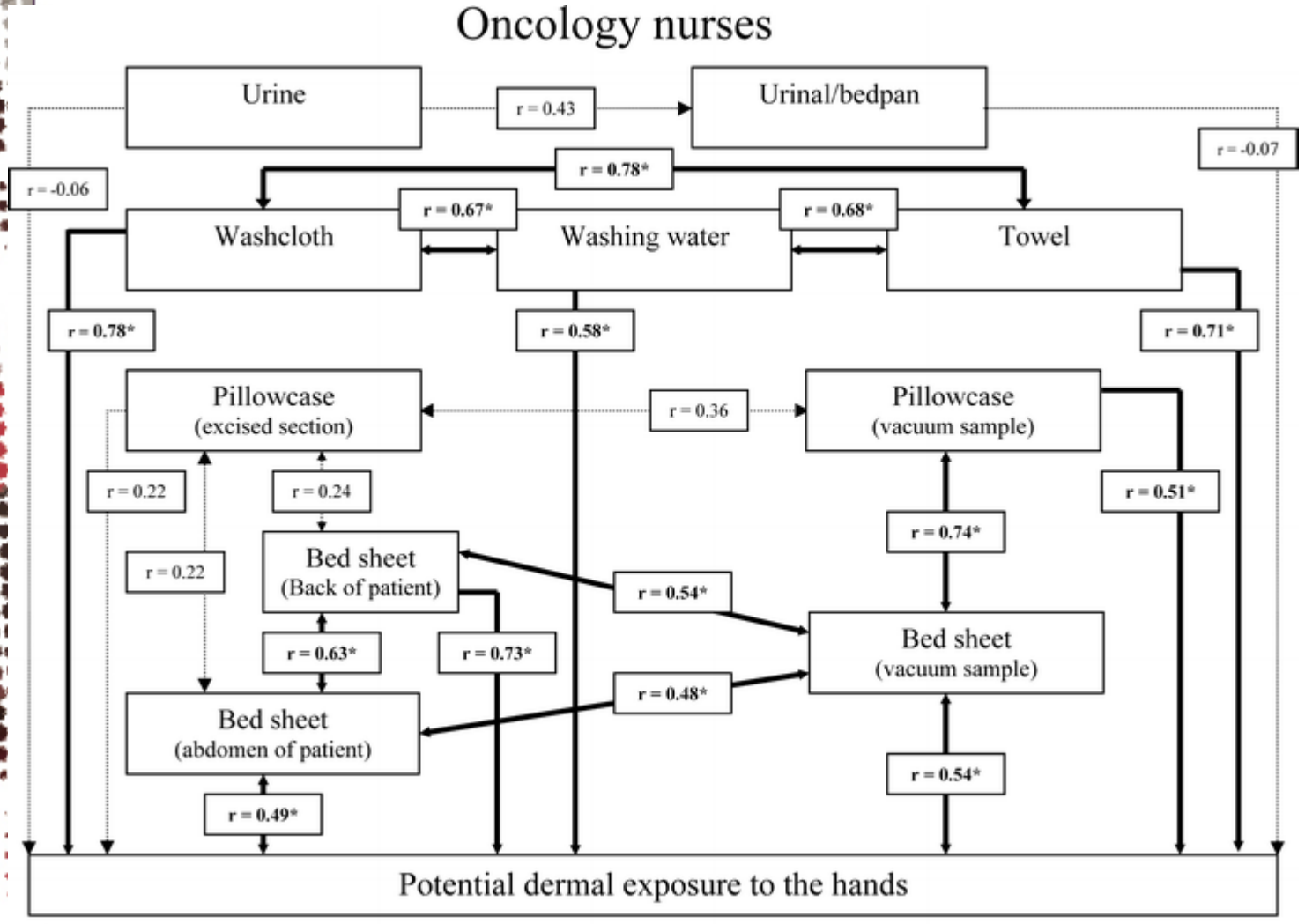


Photo Dick Ross/LINEAIR

Environments can be quite different

Exposure Assessment



* P<0.05

Exposures might not occur in a simple manner

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

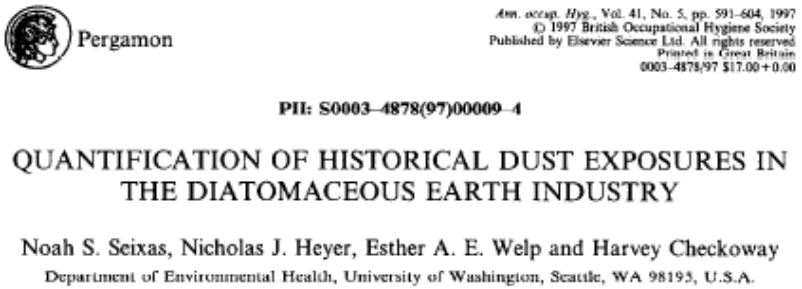
Early examples

- Dement et al. Exposures and mortality among chrysotile asbestos workers. Part I: exposure estimates. Am J Ind Med. 1983

- 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.s.o. personally
- They had to deal with changes in measurement methods over time

Early examples

- Seixas et al Ann Occup Hyg. 1997;41: 591-604. Quantification of historical dust exposures in the diatomaceous earth.



Pergamon

Ann. occup. Hyg., Vol. 41, No. 5, pp. 591–604, 1997

0003-4878/97 $17.00+0.00

PII: S0003–4878(97)00009–4

QUANTIFICATION OF HISTORICAL DUST EXPOSURES IN THE DIATOMACEOUS EARTH INDUSTRY

Noah S. Seixas, Nicholas J. Heyer, Esther A. E. Welp and Harvey Checkoway
Department of Environmental Health, University of Washington, Seattle, WA 98195, U.S.A.

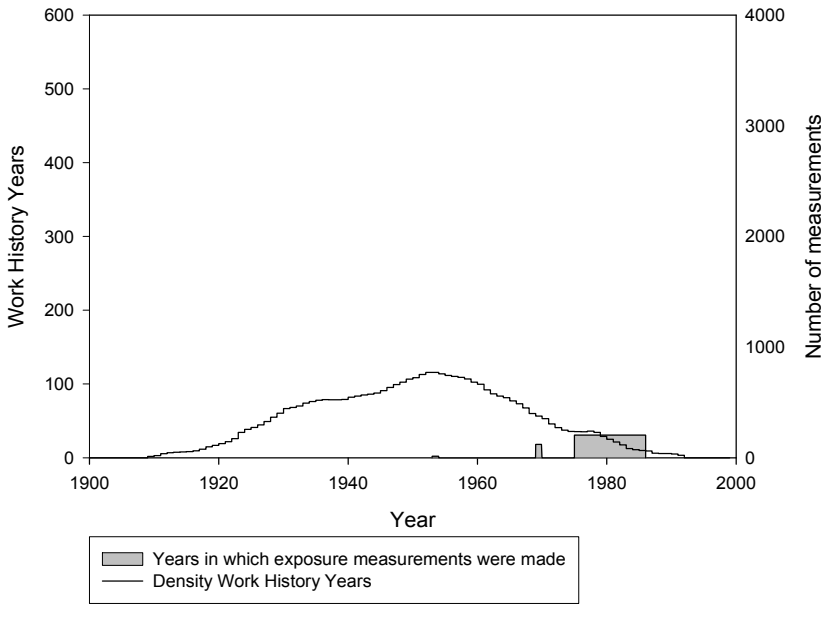
- Exposure data: 6395 records covering 1948-1988
- Conversion factors
- 0.37 mg/m^3 in 50-ies 0.17 later
- Considerable amount of extrapolation needed

Are we critical enough in evaluating epi-evidence

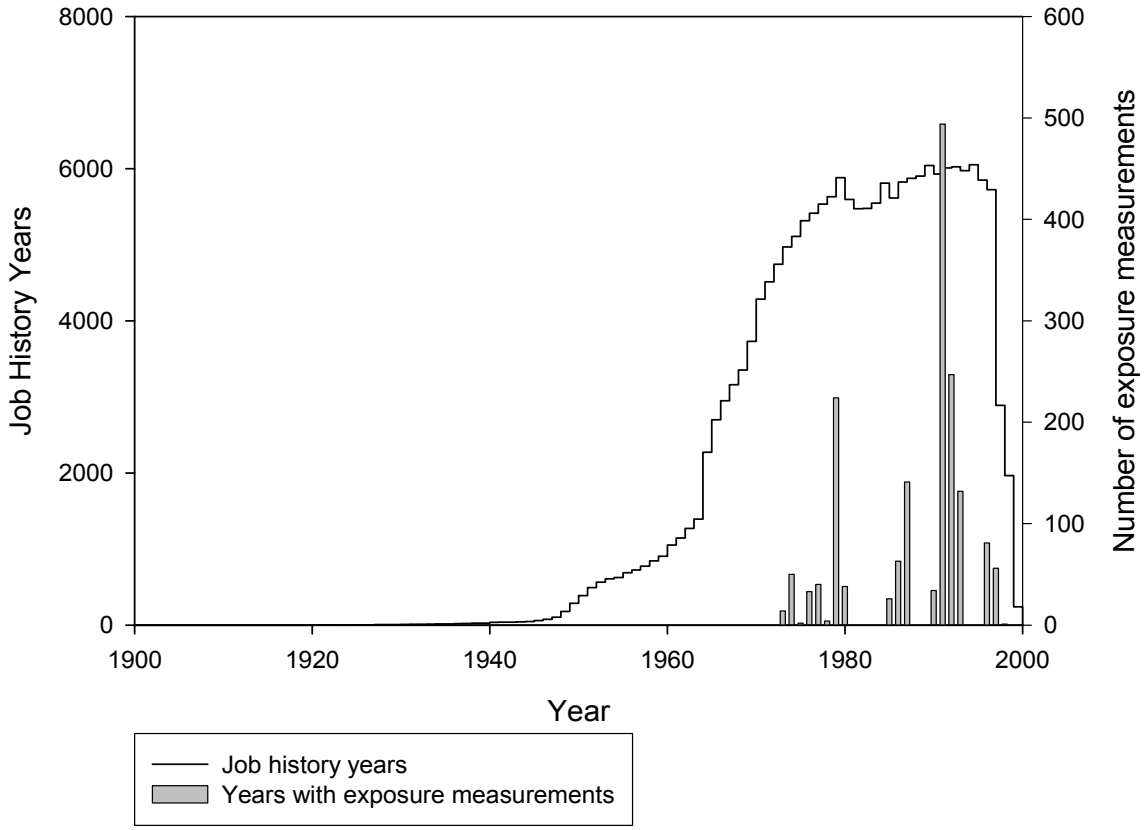
- A lot of guessing and extrapolation is going on, but are we actually aware of this?
- Let's have a look at a couple of very important epi-studies on benzene and leukemia

Work history years density plot
Australian benzene study

Work history years density plot
Canadian benzene cohort

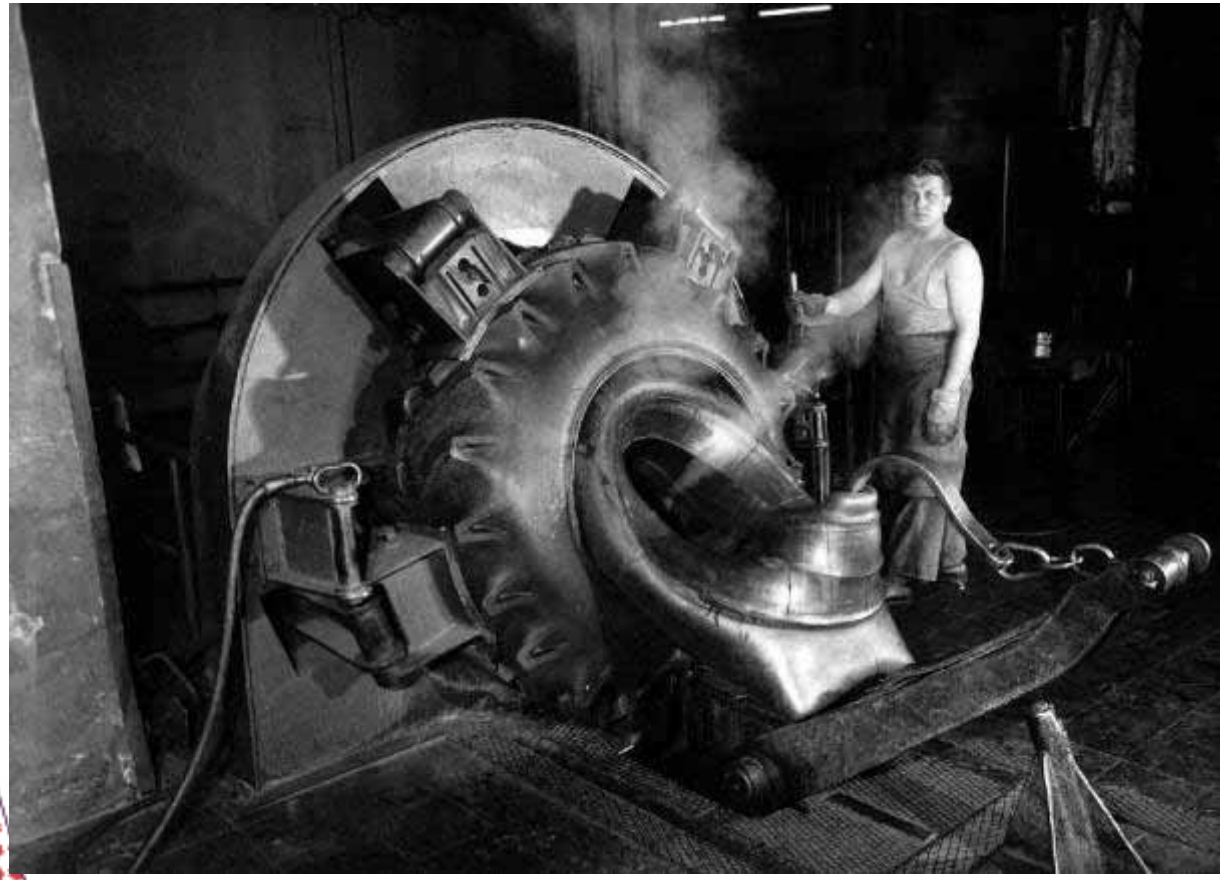


Combined asphalt cohort job history year density plot / number of exposure measurements per year



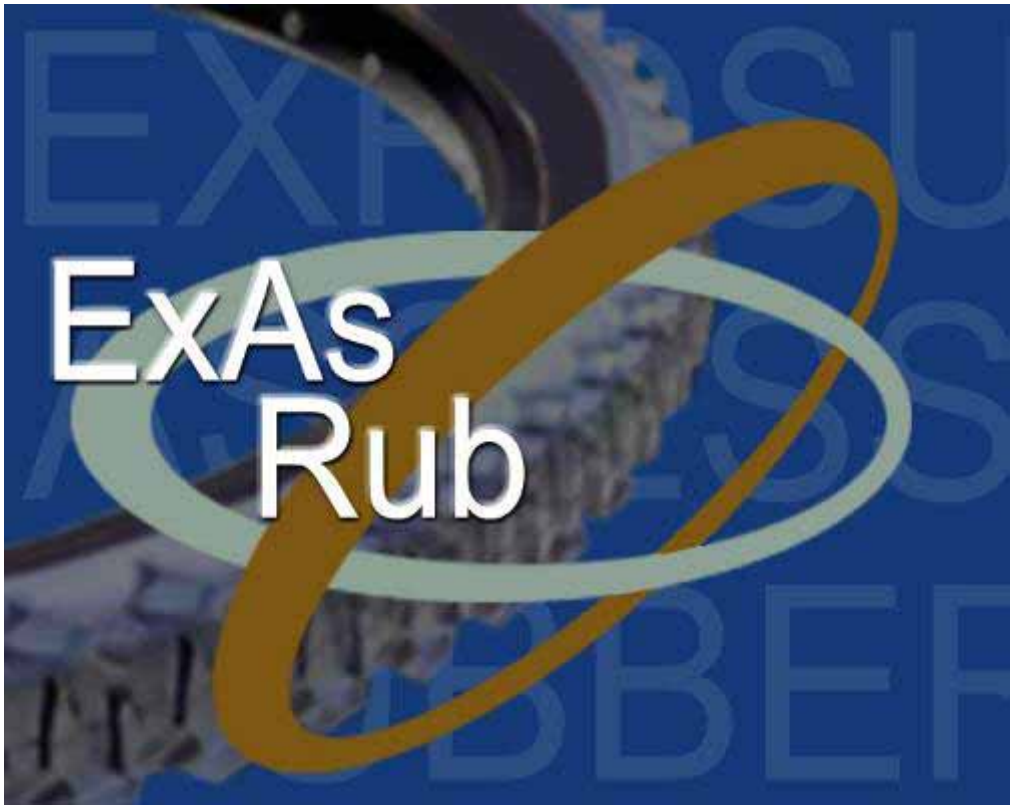
Is there any measurement data around in the first place?

The EXASRUB Project



Power of industry-wide databases

Improved Exposure Assessment for Prospective Cohort Studies and Exposure Control in the Rubber Manufacturing Industry



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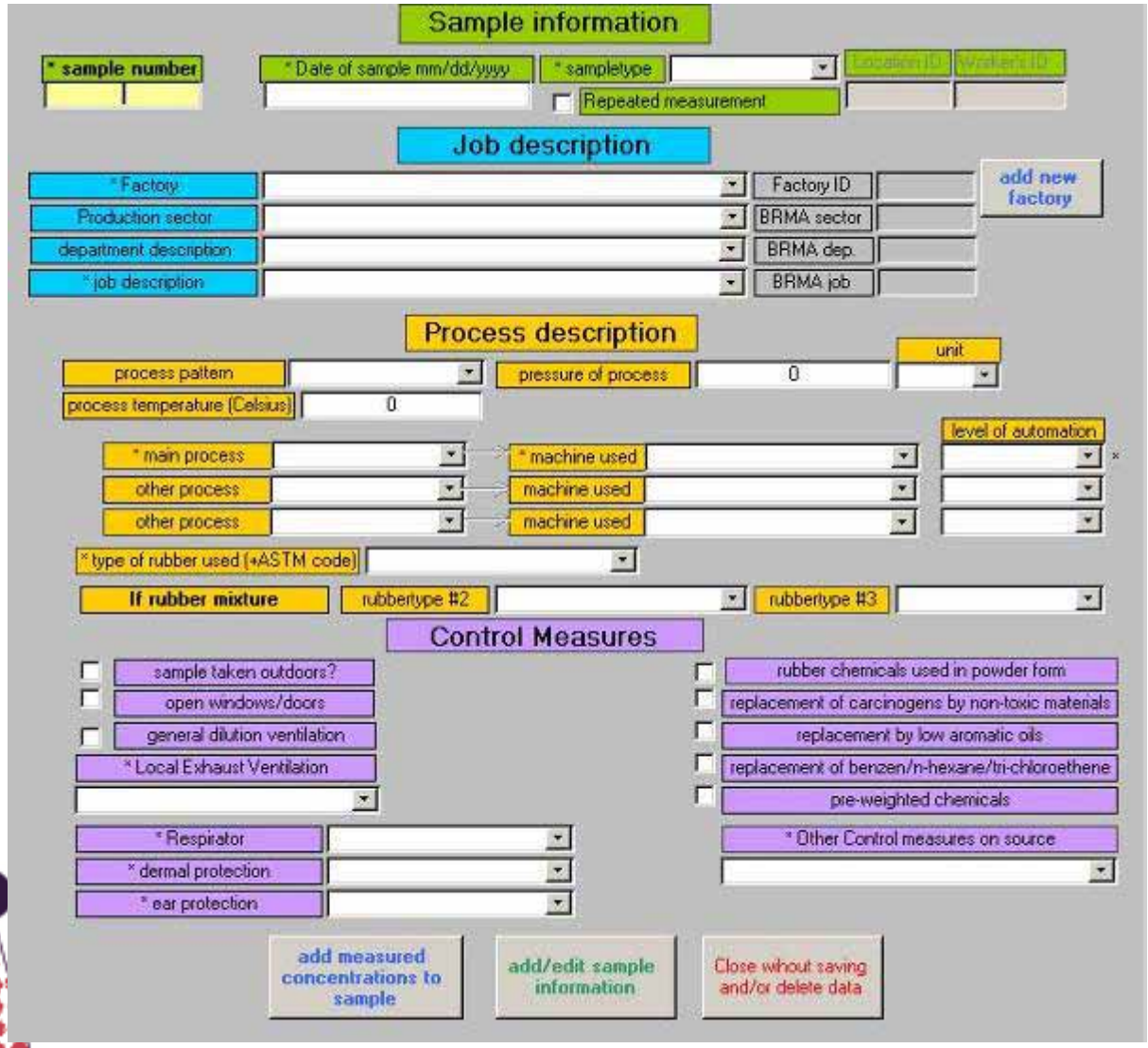
Power of industry-wide databases: ExAsRub

- 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

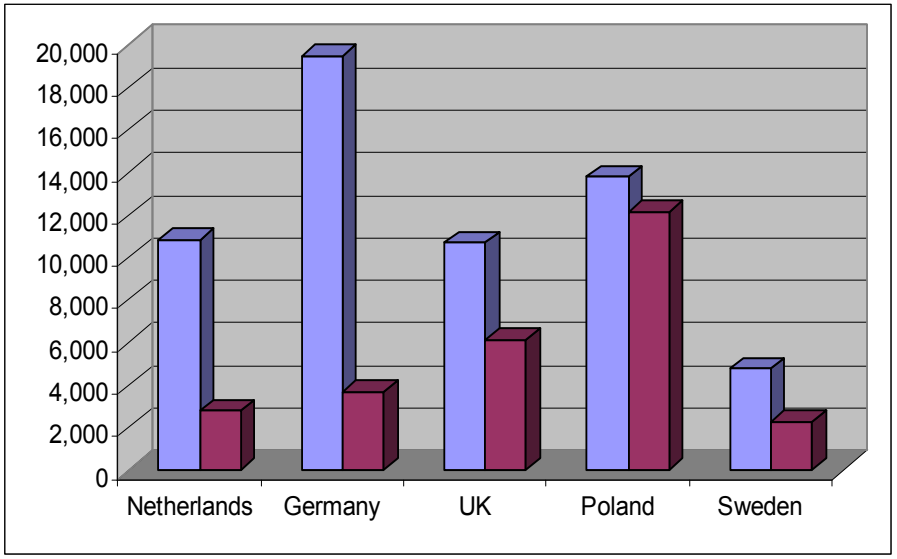
The EXASRUB interface: *Data Entry*



Power of industry-wide databases
Measurements and samples by country

N = 59.609

N(ind) = 27.095



Individual Measurements

Independent samples

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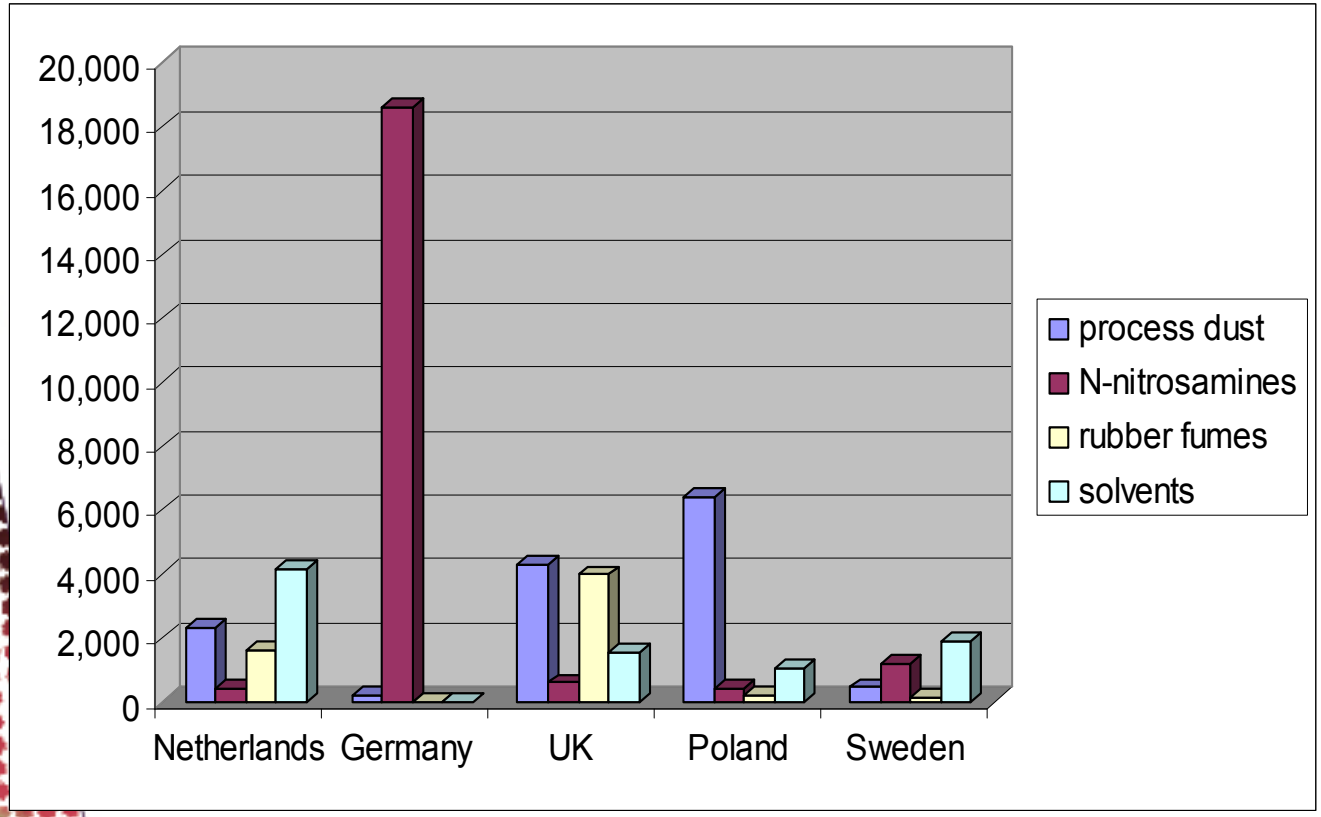
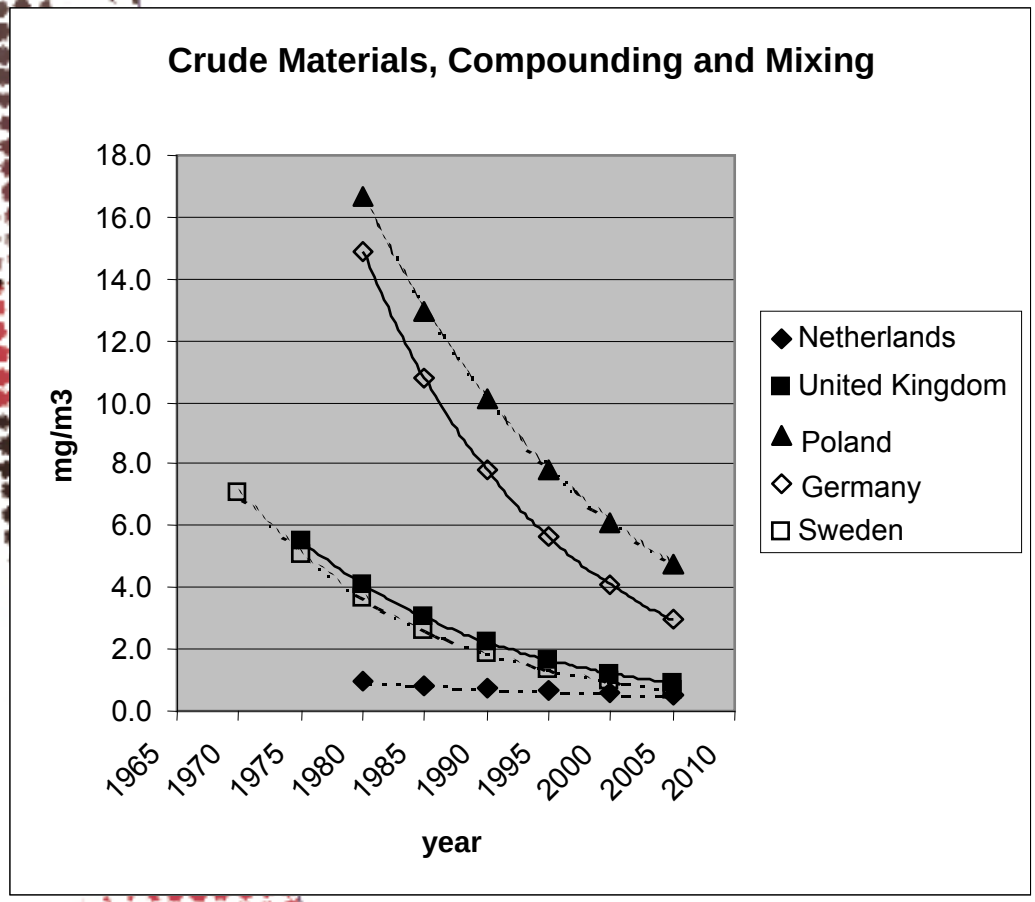
Power of industry-wide databases main agents

N_{dust} = 13.655 $N_{nitrosamines}$ = 21.202

N_{fumes} = 5.932 $N_{solvents}$ = 5.932



Power of industry-wide databases



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

	Men				Women			
Status	**Cases**		**Controls**		**Cases**		**Controls**	
	N	%	N	%	N	%	N	%
AUT	2659	49.6	2702	50.4	521	48.8	547	51.2
EAGLE	1538	48.7	1617	51.3	408	45.0	499	55.0
HdA	839	50.0	839	50.0	165	50.0	165	50.0
INCO	2057	50.5	2013	49.5	576	45.5	689	54.5
INCO_UK	281	32.9	574	67.1	161	31.9	344	68.1
LUCA	310	50.7	302	49.3	0	0.0	0	0.0
LUCAS	1042	30.6	2364	69.4	0	0.0	0	0.0
PARIS	161	42.4	219	57.6	12	44.4	15	55.6
ROME	296	52.7	266	47.3	51	34.0	99	66.0
TURIN	956	43.3	1253	56.7	176	37.0	300	63.0
TOTAL	**10139**	**45.5**	**12149**	**54.5**	**2070**	**43.8**	**2658**	**56.2**

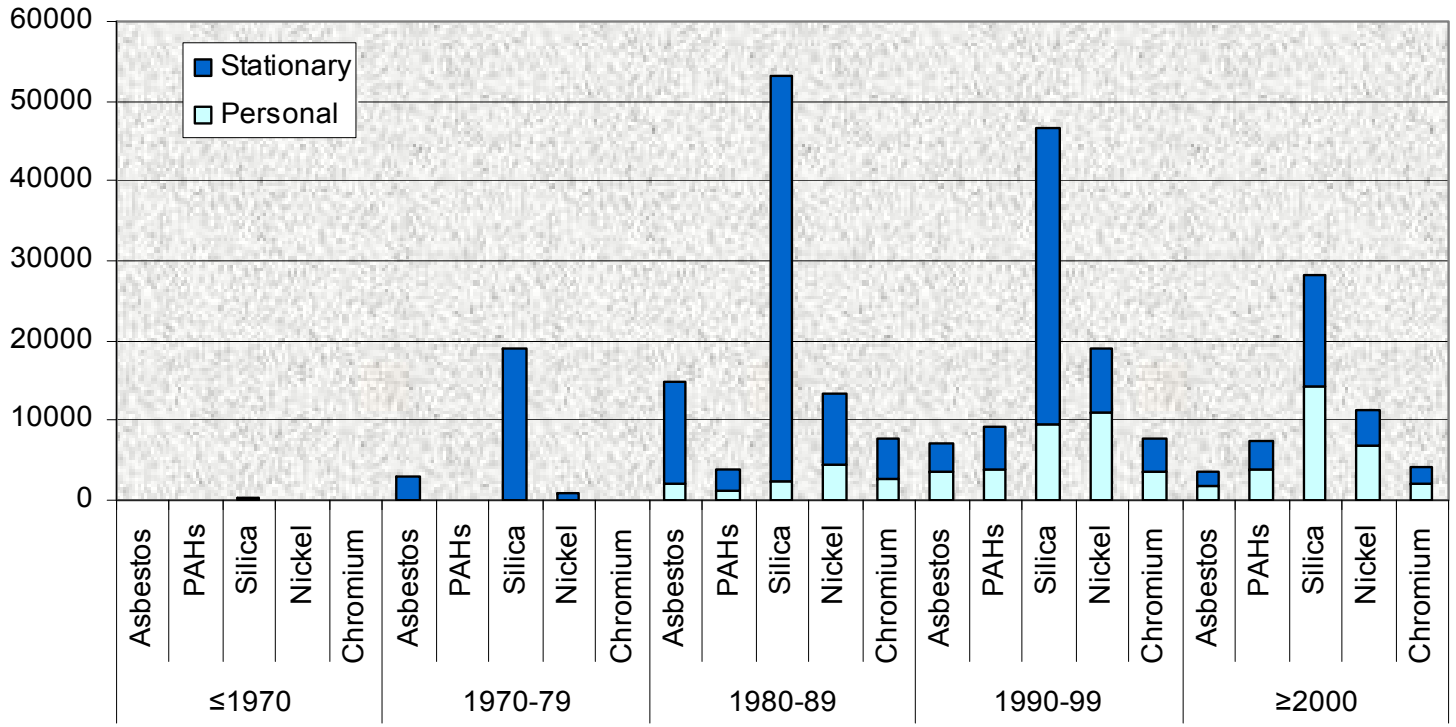
Mean job periods by sex and study

	Men		*Women*	
job periods	**Cases**	**Controls**	**Cases**	**Controls**
	Mean (min – max)	**Mean (min – max)**	**Mean (min – max)**	**Mean (min – max)**
AUT	4.06 (1-18)	4.11 (1-19)	3.75 (1-17)	3.73 (1-16)
EAGLE	2.48 (1-14)	2.54 (1-13)	2.12 (1-10)	2.12 (1-10)
HdA	5.23 (1-31)	5.35 (1-24)	4.85 (1-18)	4.76 (1-20)
INCO	3.18 (1-21)	3.17 (1-15)	2.78 (1-13)	2.81 (1-13)
INCO_UK	4.69 (1-21)	5.03 (1-20)	4.54 (1-17)	4.66 (1-18)
LUCA	3.12 (1-11)	3.02 (1-12)	-	-
LUCAS	2.40 (1-10)	2.69 (1-9)	-	-
PARIS	1.91 (1-5)	1.80 (1-5)	1.88 (1-5)	1.56 (1-4)
ROME	2.10 (1-8)	2.10 (1-7)	1.39 (1-4)	1.31 (1-3)
TURIN	3.25 (1-15)	3.43 (1-17)	2.70 (1-13)	2.28 (1-11)

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?



What will we get?

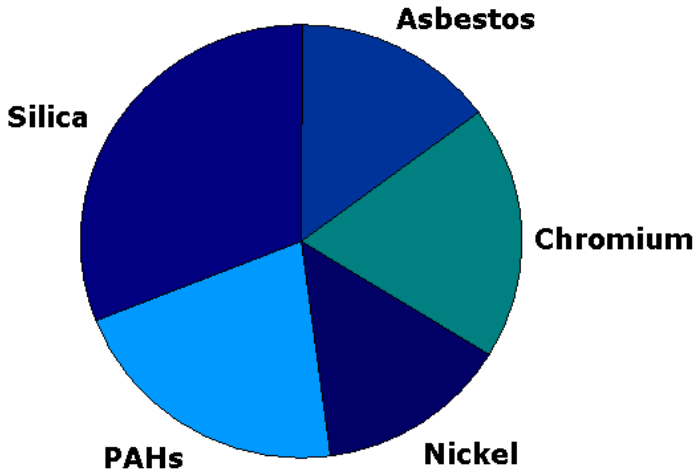
- A lot, but some data owners are not easily to persuade handing over their individual measurement results together with contextual information
- Individual data needed, because we will have to make adjustments for differences in measurement strategy, measurement devices, analytical procedures etc.
- Turns out that getting data from insurance type institutions like BGIA (MEGA database with more than 2 million meausments) 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

Time Period	Working years	%
<1970	610,582	48%
1970-1979	274,439	22%
1980-1989	244,829	19%
1990-1999	122,892	10%
≥2000	11,851	1%
Total	**1,264,593**	**100%**

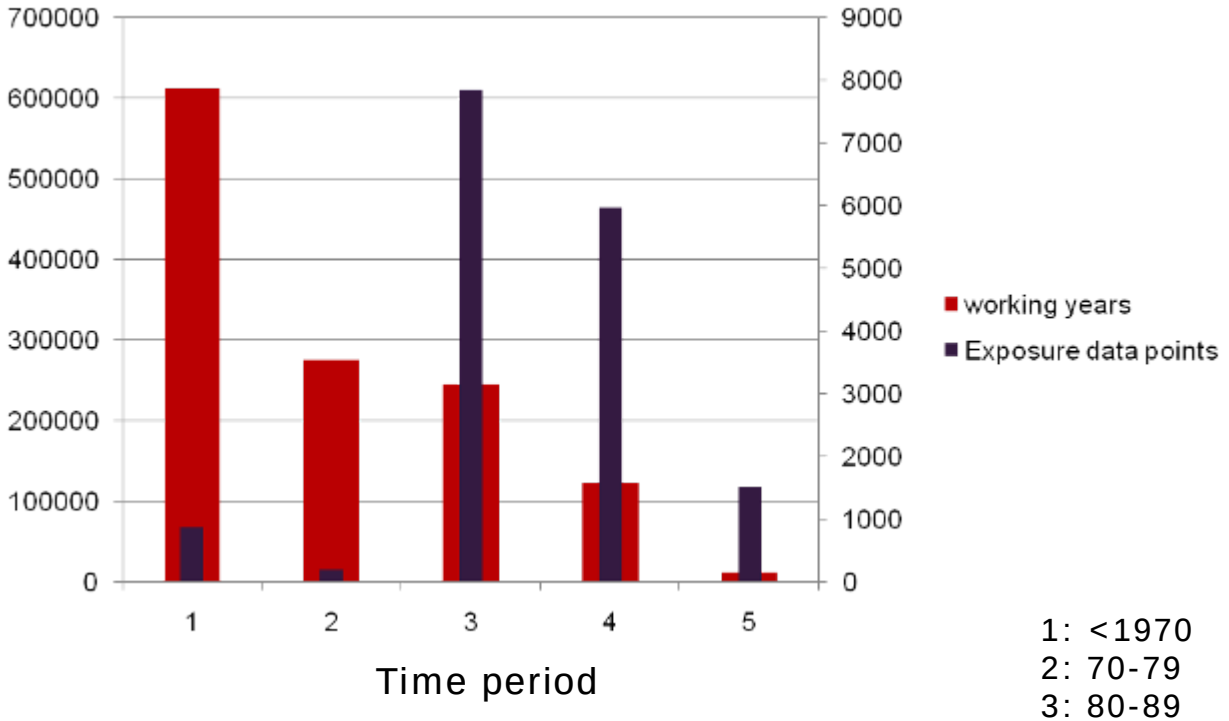
For 359 job periods the time period unknown

Overlap Working Years – Data Points

Time Period	Working years	Number exposure data points
<1970*	610,582	859
1970-1979	274,439	177
1980-1989	244,829	7,846
1990-1999	122,892	5,966
≥2000	11,851	1,506
Total	**1,264,593**	**16,384**

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

Overlap Working Years – Data Points (by time period)



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

Distribution Working Years

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

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:

	# cases	# controls	OR	95%CI
Never	6975	9300	1.00	
Low	3975	4473	1.14	1.08-1.20
High	1256	1034	1.45	1.33-1.59

I guess we needed a challenge!

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)!

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

Building an industry-wide occupational exposure database for respirable mineral dust

Experiences from the IMA Dust Monitoring Programme

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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

Status of participation

Winter 2000/2001 – Summer 2007

13 campaigns

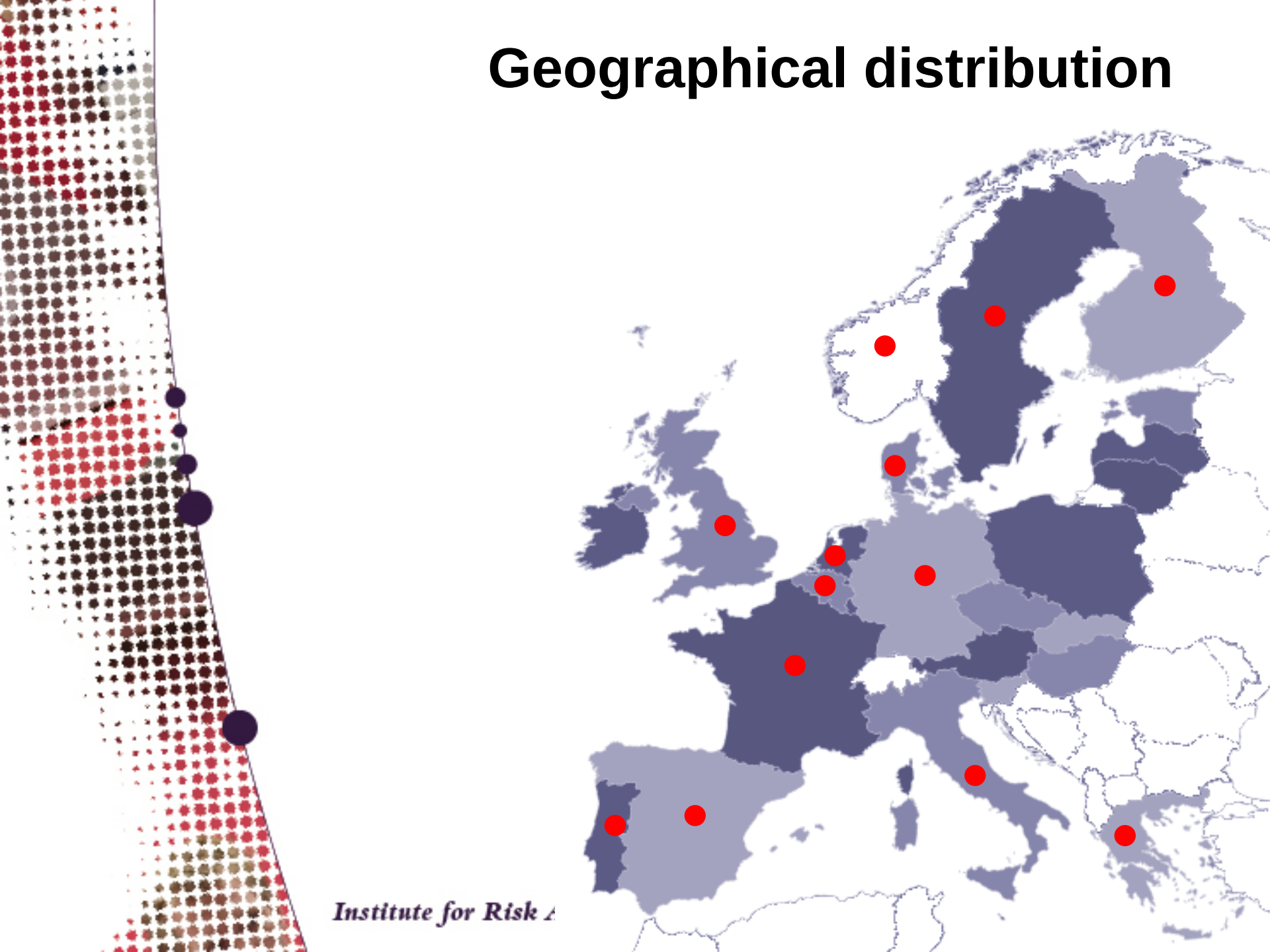
24 companies (several SME's)
85 sites

13 countries

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

~ 5000 workers
(2000 monitored)

Geographical distribution



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Company

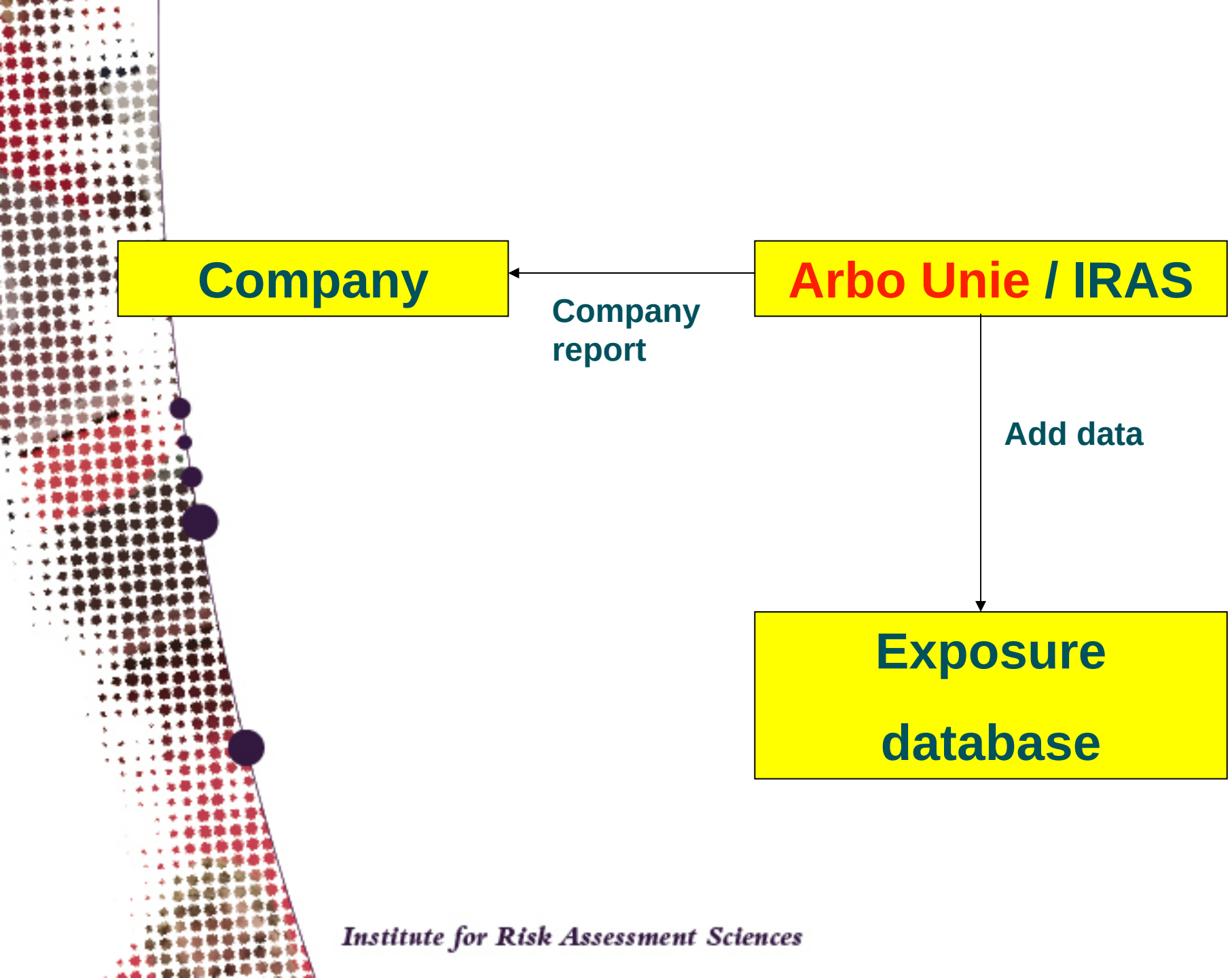
Sampling by:
- Company representatives
- External IH / laboratory

Company

Submit data

Arbo Unie / IRAS

- Extensive data check
- If needed communication with company representatives


Company
Arbo Unie / IRAS
Company report
Add data
Exposure database

Company

Arbo Unie / IRAS

IMA-Europe

Yearly

Exposure database

Analyses of pooled data

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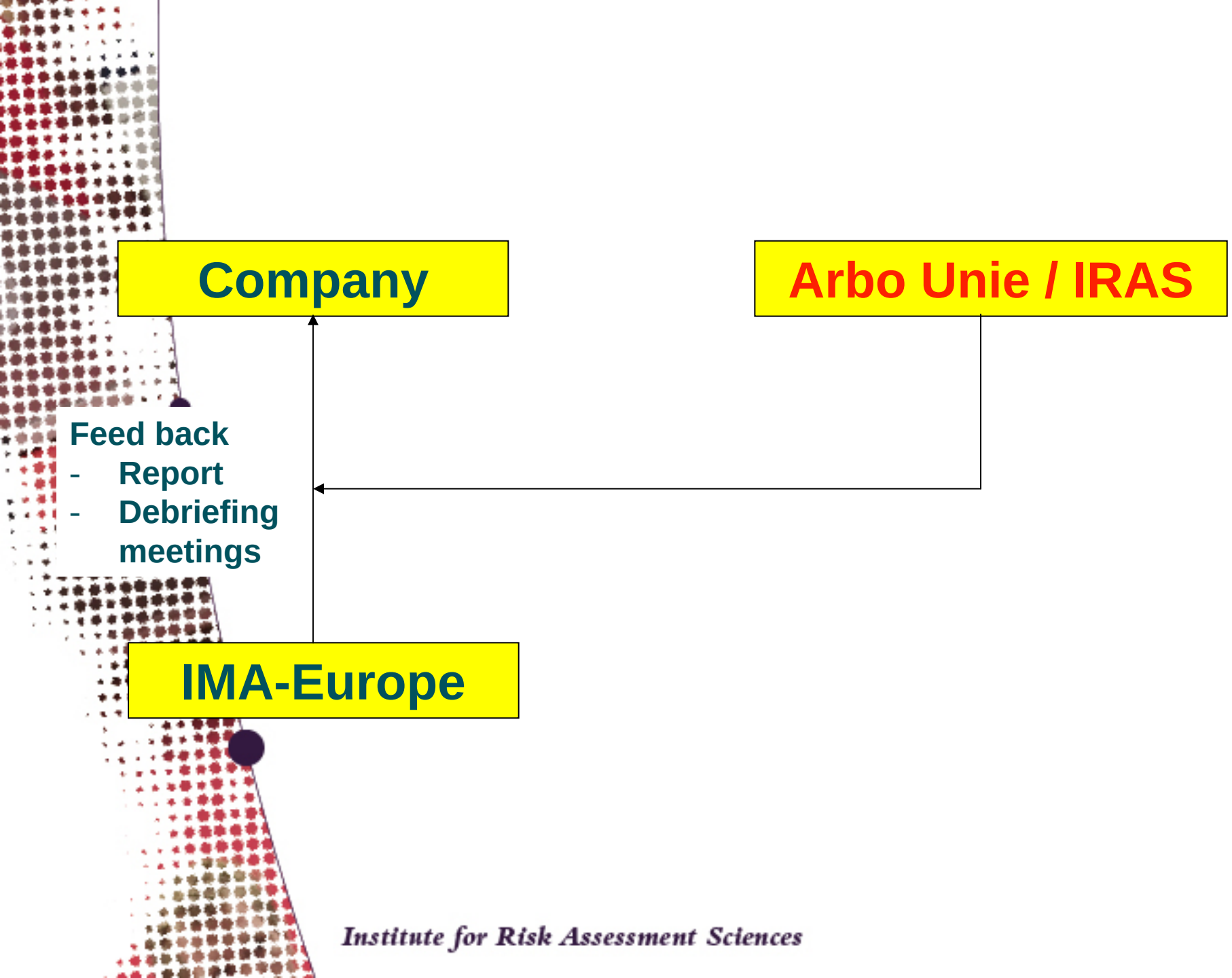
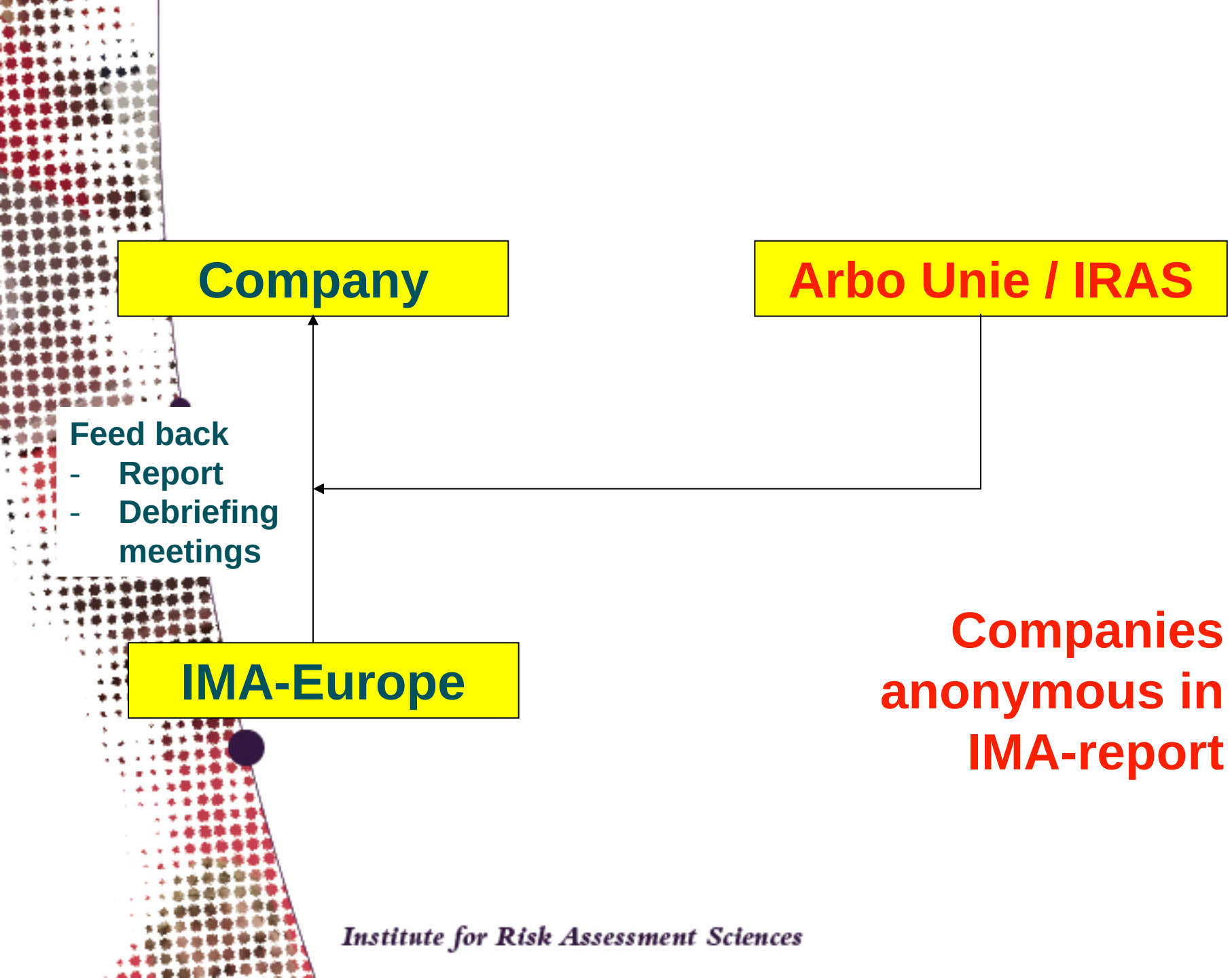

Company
Arbo Unie / IRAS
Feed back
- Report
- Debriefing meetings
IMA-Europe


Company
Arbo Unie / IRAS
Feed back
- Report
- Debriefing meetings
IMA-Europe
Companies anonymous in IMA-report
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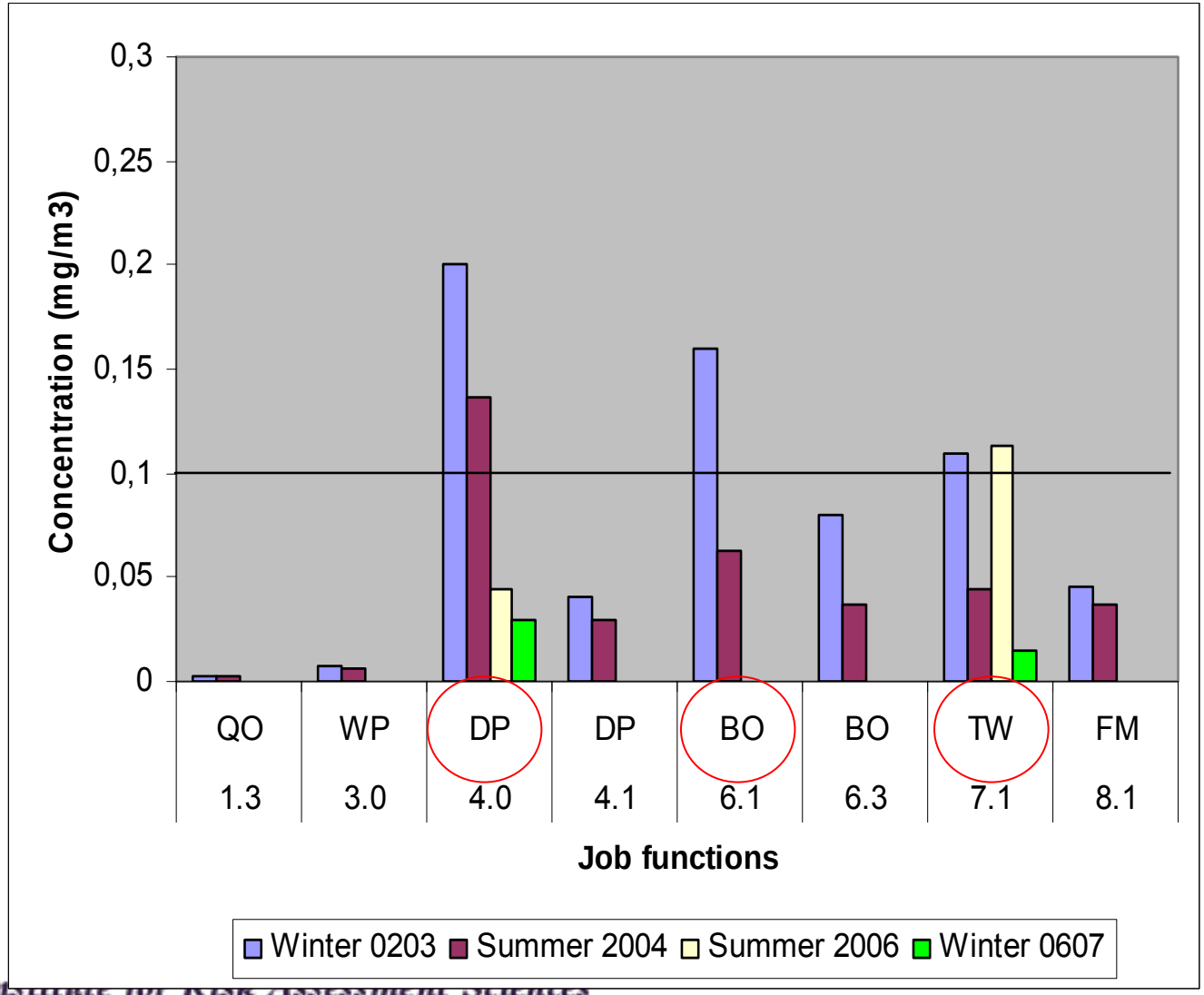
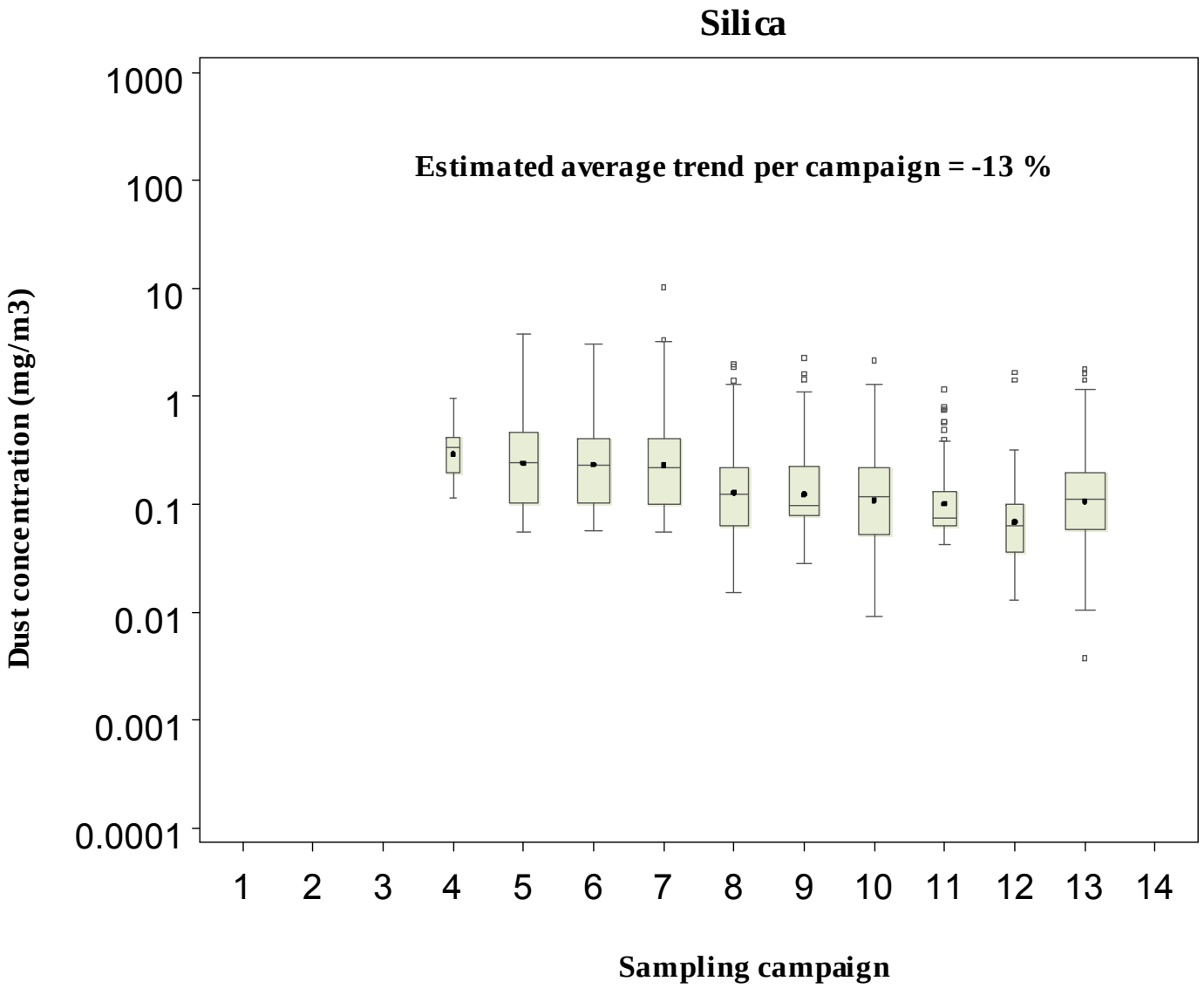
Expample of site report

Geometric mean quartz exposure

Example:

Time trends visible

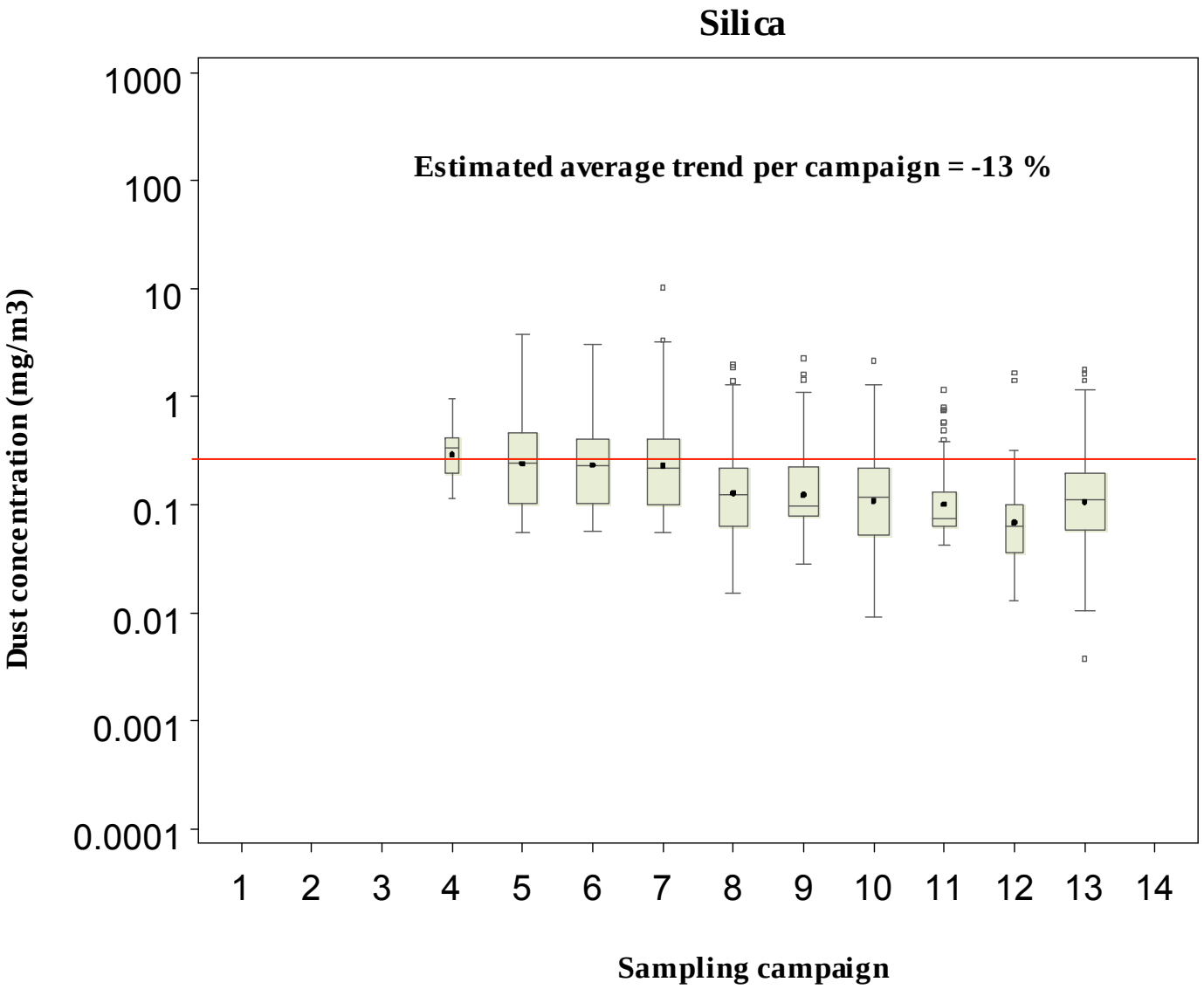




Respirable dust !

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.



Respirable dust !

95% CI:
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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)