Assessing exposure to occupational chemicals in large-scale epidemiological studies on occupational cancers

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Industrial Cohort Study
European Asphalt Workers

Community-based (case-control) studies

SYNERGY

Pooled case-control studies on lung cancer

Background

- Health concerns in asphalt industry
  - Obstructive respiratory diseases
  - Dermatitis
  - Acute irritation
  - Neurological symptoms
  - Tar and lung cancer (tar use banned in EU)
  - Bitumen and lung cancer?
- Main issue: is bitumen fume a human carcinogen?
  - IARC Volume 35, 1984, Suppl. 71987: Current evidence inadequate

Objectives

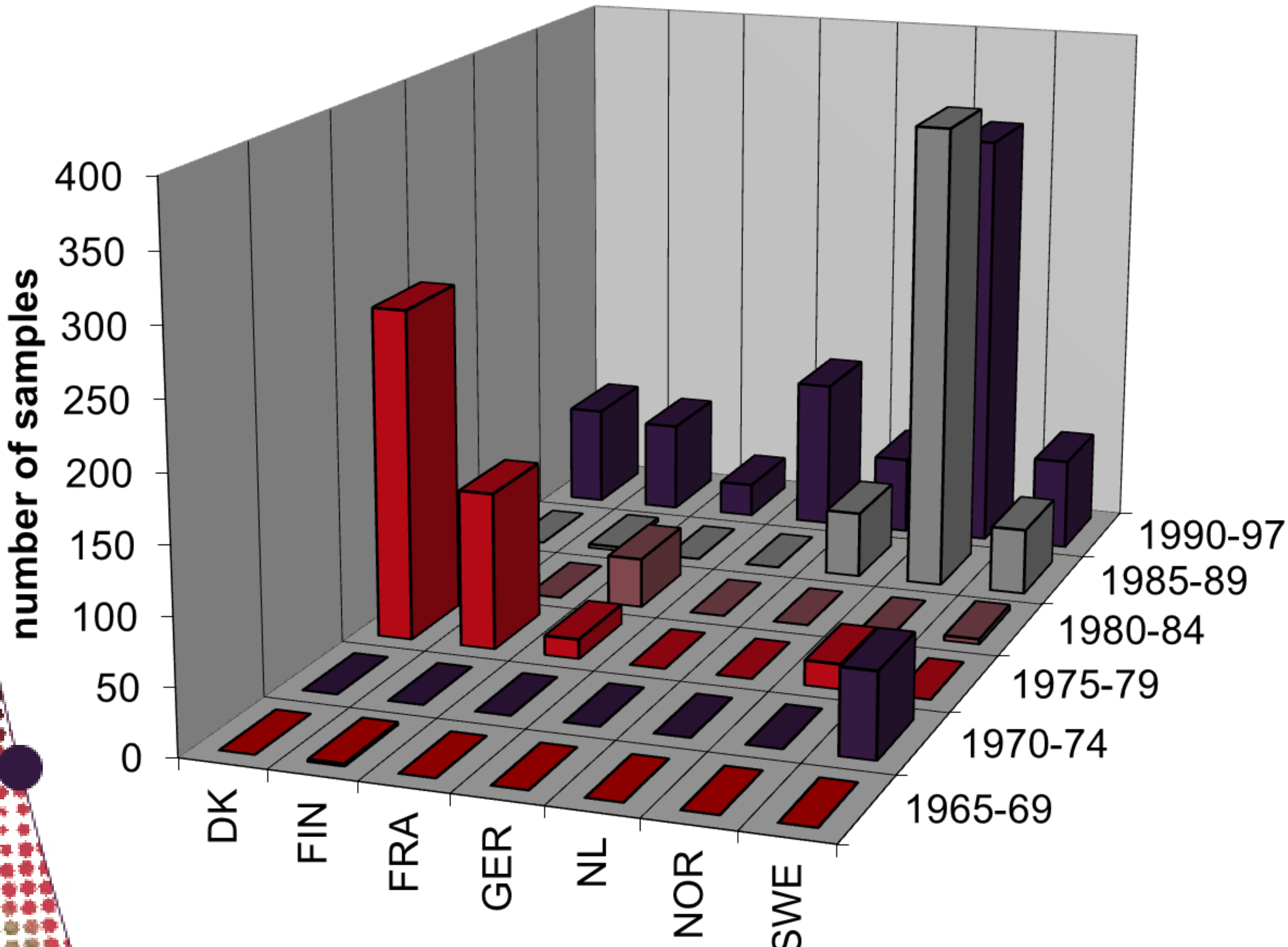
- IARC initiated multi-centric international mortality study of European asphalt workers
- Phase I: historical cohort
- Phase II: nested case-control study
- Goal: assess whether bitumen fume *per se* is carcinogenic
- Develop coordinated exposure assessment

Exposure reconstruction

- Specific goal: estimates for known and suspected carcinogens that are company-, time period- and job-specific
- Resources
  - Exposure measurements
  - Company questionnaires
  - Statistical exposure models
  - Expert assessment
  - Job histories
- Produce study specific exposure matrix

Exposure measurements

- Asphalt Workers' Exposure (AWE) database
- Created for the study
- Compiled all available exposure measurements from participating countries
- Included:
  - exposure concentrations measured
  - information on determinants of exposure
  - link to company questionnaires


400
350
300
250
200
150
100
50
0
number of samples
DK
FIN
FRA
GER
NL
NOR
SWE
1990-97
1985-89
1980-84
1975-79
1970-74
1965-69

AWE database

- 34/38 data sets unpublished
- 2,007 samples
- 6,000++ measurements
- Sufficient data to model bitumen fume, organic vapour, and PAH exposures in paving
- after Feb 1997: additional USA, Italy, Germany data added; for model validation

Exposure levels

	n	GM	GSD	AM	Min	Max
Bitumen fume (mg/m^3)	1,193	0.28	6.8	1.91	LOD	260
Organic vapour (mg/m^3)	510	1.86	6.9	7.59	LOD	290
benzo(a) pyrene (ng/m^3)	487	8.58	6.8	95.8	LOD	8,000

Mixed-effects models

$$Y_{ij|\beta 1 \ldots \beta n} = \mu + \beta_1 + \ldots + \beta_n + \chi_i + \varepsilon_{ij}$$

$Y_{ij|\beta 1 \ldots \beta n}$ = natural logarithm of the exposure concentration measured on the j^{th} day of the i^{th} worker in presence of the $\beta_1 \ldots \beta_n$ determinants of exposure;

μ = mean of log-transformed exposure averaged over all determinants of exposure;

$\beta_1 \ldots \beta_n$ = fixed effects of determinants of exposure;

χ_i = random effect of i^{th} worker;

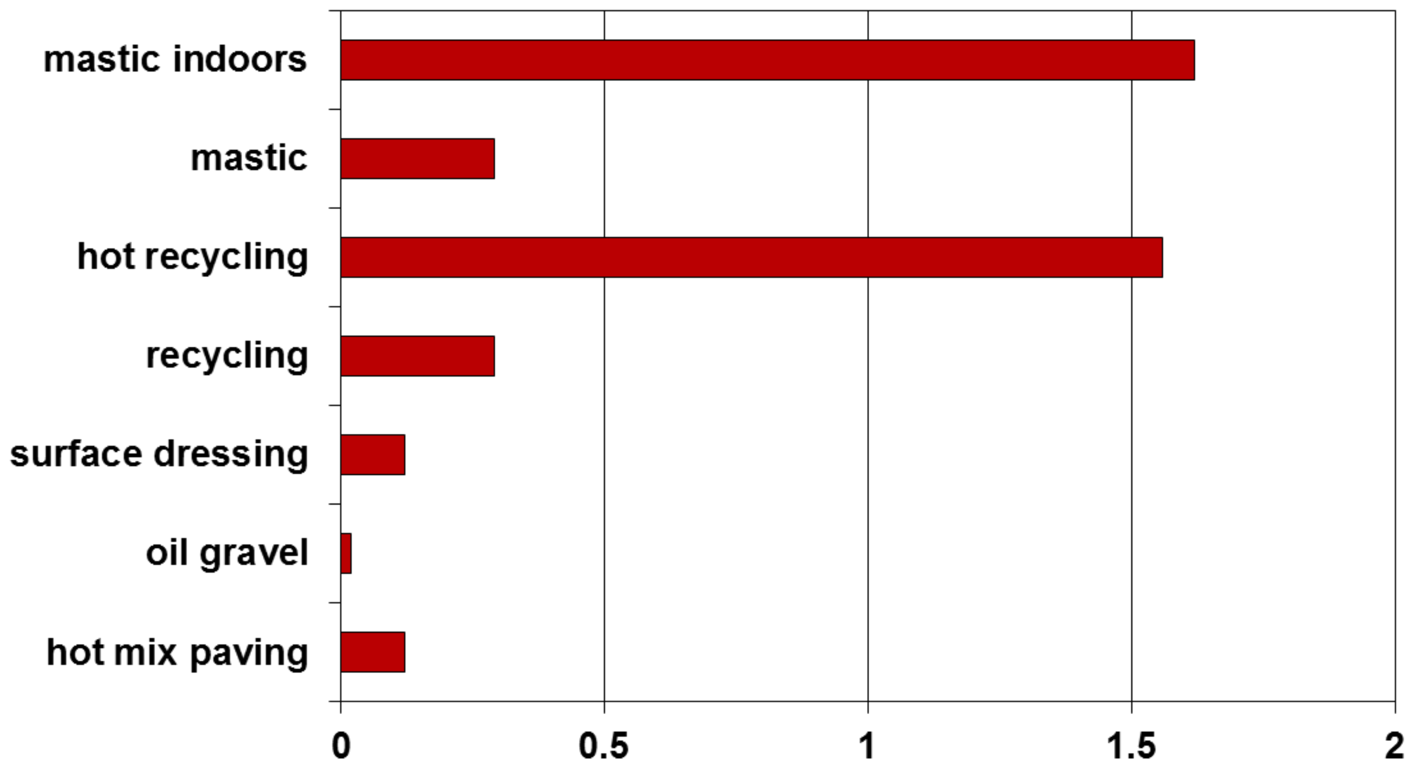
ε_{ij} = random within-worker variation.

REML algorithm, compound symmetry variance structure

Features of exposure models

- Explained
  - 40% of total variability
  - 55-80% of between-worker variability
- Time trends: -6 to -14% per year between 1970 and 1997
- Coal tar use as key predictor of benzo(a)pyrene exposure
- Differences between type of paving: 10-60 fold

Predicted medians for bitumen fume (mg/m^3) exposure in 1997 by type of paving



Model validation

- Create predictions on data not used to build exposure models
- -50 to -70% bias in bitumen fume and benzo(a)pyrene models -- acceptable
- poor precision
- suitable for group-based exposure assessment

Exposure matrix (ROCEM)

- Dimensions: company, time, job, agent
- Quantitative estimates: bitumen fume, organic vapour and b(a)p among pavers
- Semi-quantitative estimates: other jobs and agents (Si, diesel, asbestos & coal tar).
- Link company questionnaires (CQ) to statistical models
- Week-long meeting in Lyon to review CQ

Company questionnaire

Straßenbau (11)

Geben Sie bitte an, wie häufig (%)* in Ihrer Firma die folgenden Stoffe oder Techniken angewendet wurden?

Spezieller Anwendungsbereich	Vor 1960	1960-64	1965-69	1970-74	1975-79	1980-84	1985-89	1990-96
Einbau von Gußasphalt in geschlossenen Räumen	90%	80%	→	→	70%	60%	50%	45%
Einbau von Gußasphalt im Außenbereich	10%	20%	20%	20%	30%	40%	50%	65%
Remixing im Asphalt-Straßenbau vor Ort	0%	→	→	→	→	→	→	→
Aufbrechen alter Asphaltbeläge zu Recyclingzwecken	0%	→	→	→	→	→	10%	10%
Einbau von Beton	0%	→	→	→	→	→	→	→

Unser Anliegen ist es, den durchschnittlichen Zeitanteil zu ermitteln, den Arbeiter im Straßenbau mit den genannten Stoffen/Techniken zubringen*. Sollten beispielsweise 95% der Straßenbauer Ihrer Firma mit heißem Asphalt-Mischgut arbeiten und 5% mit Gußasphalt, so betrüge die Häufigkeit 5%, mit der Gußasphalt angewendet wird.

*** Falls nur ein Teil der Beschäftigten die genannte spezielle Tätigkeit ausgeführt hat, ist der Prozentwert entsprechend zu reduzieren.**

Semi-quantitative assessment

- Time trends and effects of coal tar from statistical models
- Else: consensus of a panel of occupational hygienists on relative exposure intensity in different jobs
- Generic rules with few assumptions that were applied across companies and time periods

Quantitative Assessment 1

X_{ij} = the median value of the long-term means of individual exposures of a group of workers during exposure scenario *i* in a given time interval *j*:

$$X_{ij} = \exp(LM_{ij} + ½ S^2_{ww})$$

LM_{ij} = model-predicted logarithmic mean;

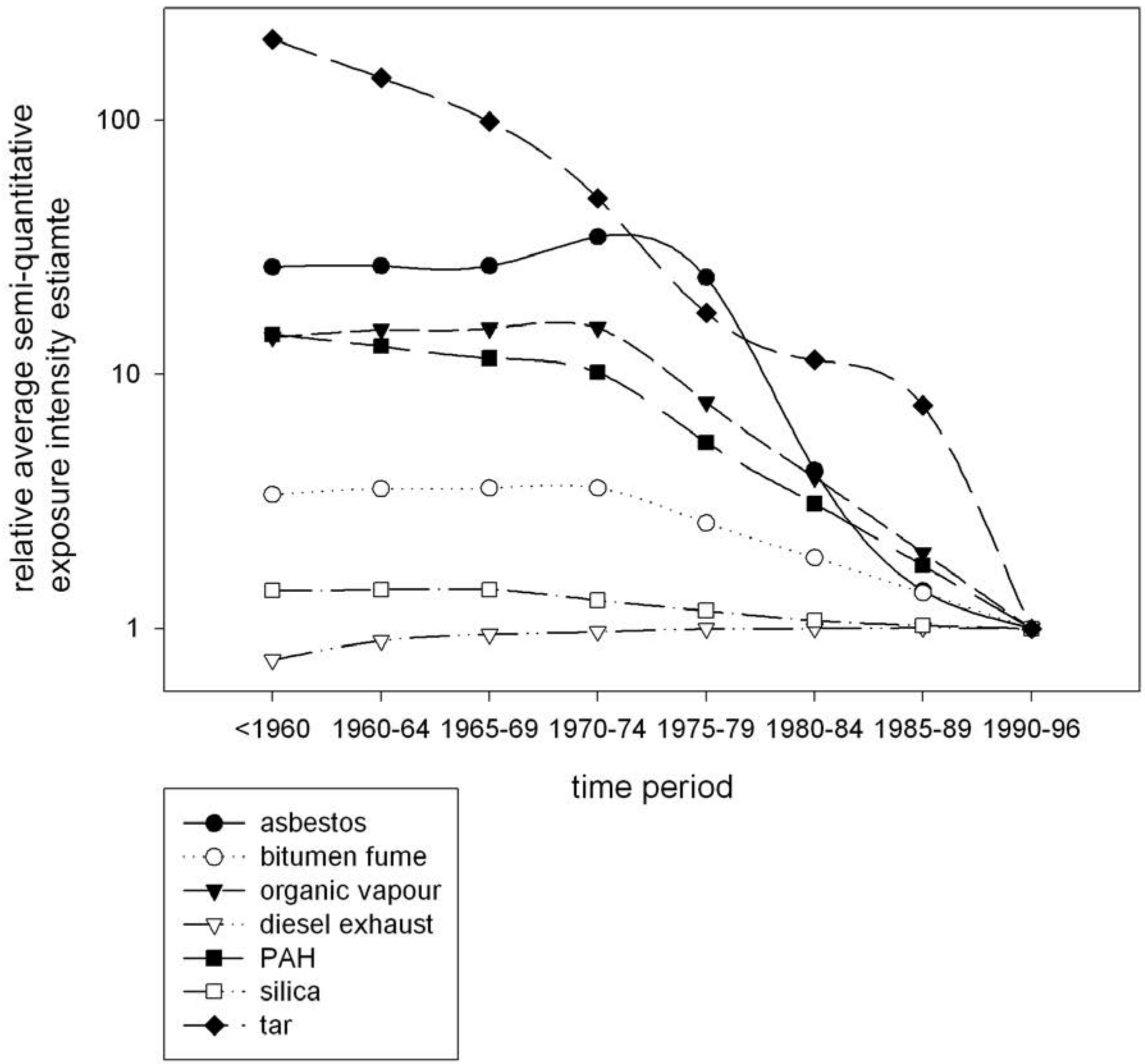
S^2_{ww} = estimate of day-to-day logarithmic variance

Quantitative Assessment 2

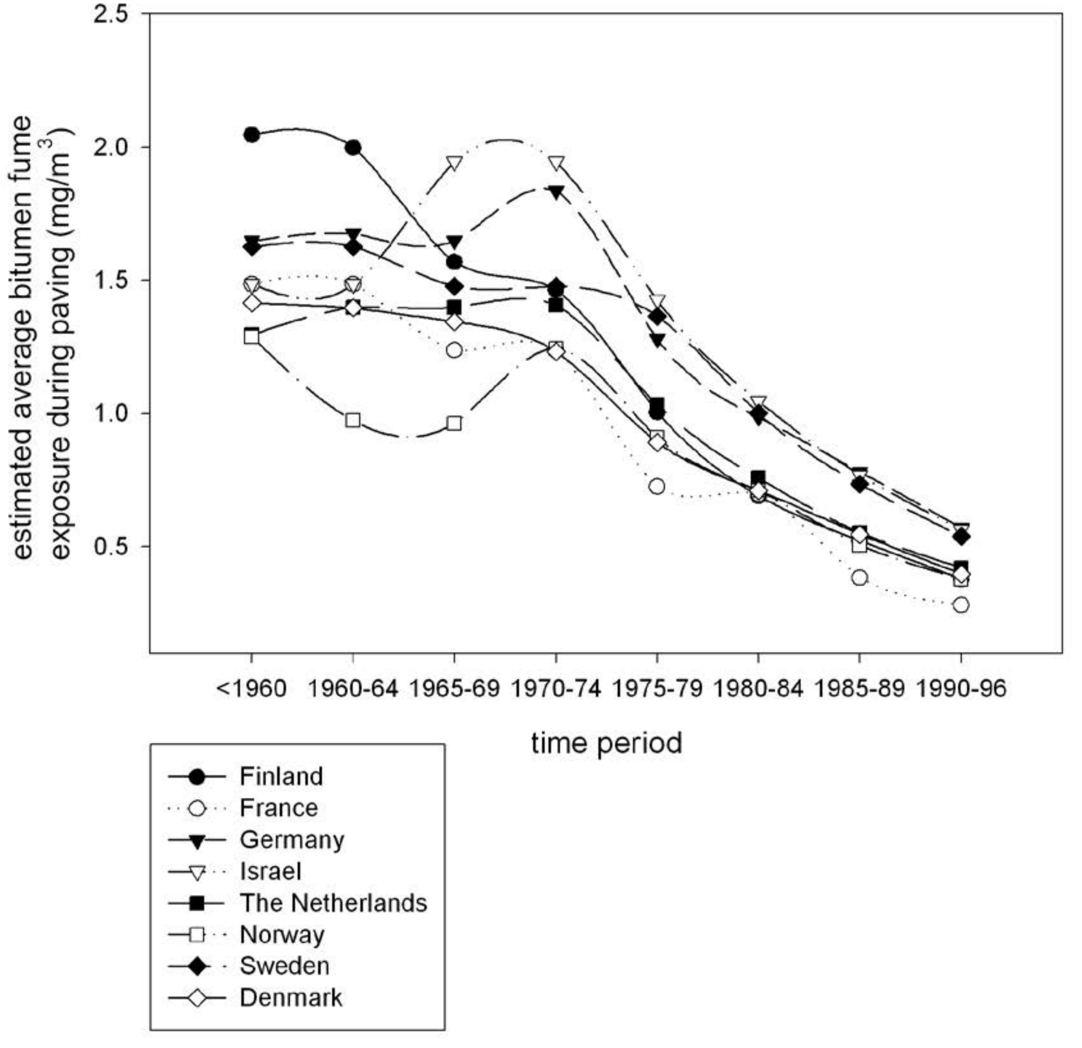
Mean exposure (M_j) for a group of workers who experiences *i* exposure *scenarios* in a given time interval *j*:

$$\mathbf{M_j = \Sigma \{X_{ij} \times f(S_{ij})\}}$$

$f(S_{ij})$ = frequency of scenario *i* during time interval *j*.



relative average semi-quantitative
exposure intensity estiamte
100
10
1
<1960
1960-64
1965-69
1970-74
1975-79
1980-84
1985-89
1990-96
time period
asbestos
bitumen fume
organic vapour
diesel exhaust
PAH
silica
tar



estimated average bitumen fume exposure during paving (mg/m3)
2.5
2.0
1.5
1.0
0.5
<1960
1960-64
1965-69
1970-74
1975-79
1980-84
1985-89
1990-96
time period
Finland
France
Germany
Israel
The Netherlands
Norway
Sweden
Denmark

Cohort description

- 8 countries, 217+ companies
- Males only
- One full working season = inclusion criteria
- Company records, except in Sweden
- 29,820 workers ever employed in bitumen-exposed jobs
- 32,245 ground and building construction workers
- 17,757 workers not classifiable

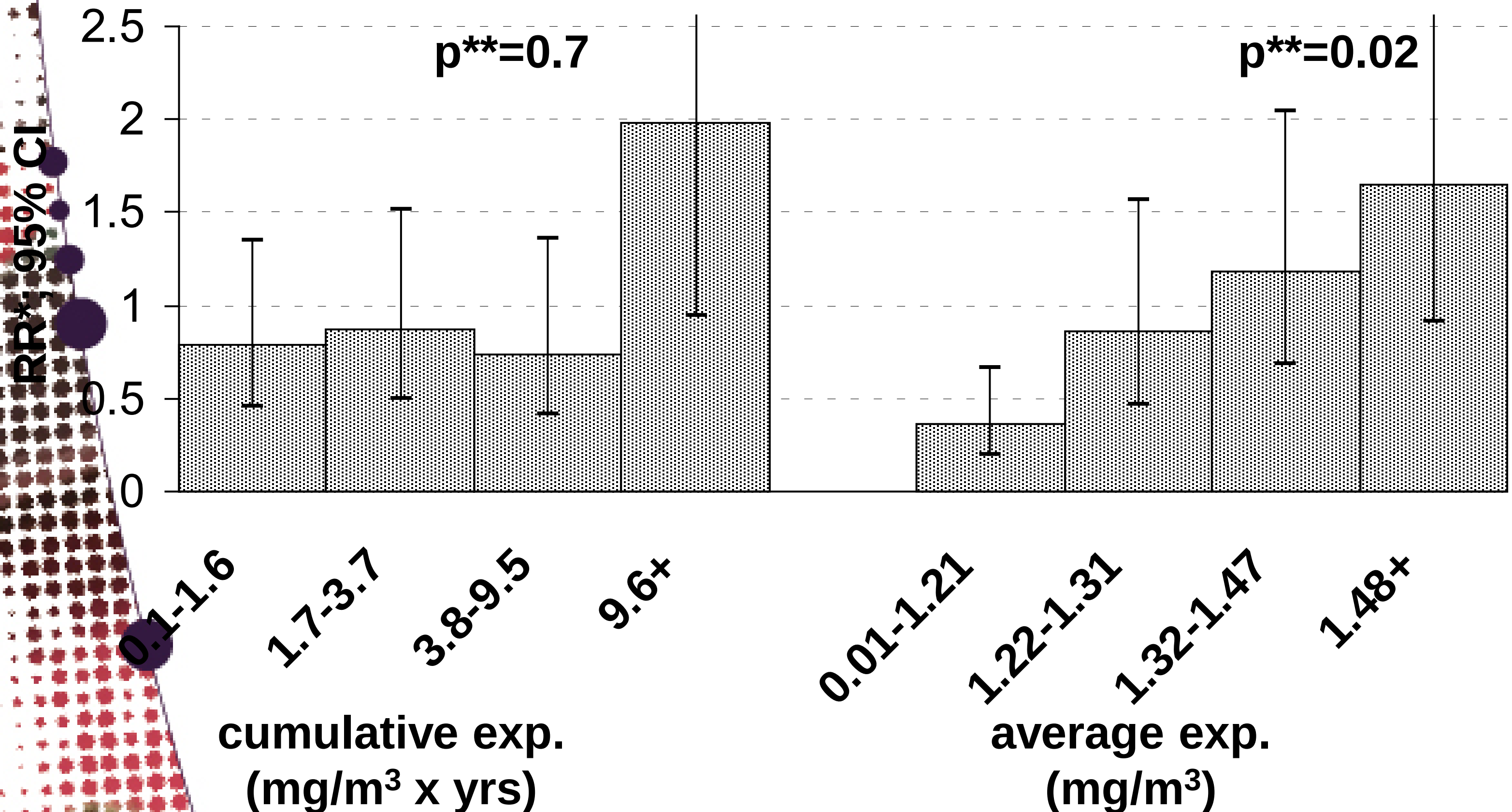
Cohort description

- Denmark: 32% bitumen workers, Norway & Sweden: 15-19%, etc.
- Mortality follow-up: 1953-2000
  - mean duration: 16.7 years
- 1,287,209 person years total
- 481,089 person-years: bitumen workers
- Loss to follow-up: 0.7%, emigration: 0.5%

Compare to general population

Cause	Ever bitumen worker			Only construction worker		
	O	SMR	95%CI	O	SMR	95%CI
All	3987	.96	.93-.99	3876	.91	.88-.94
All cancer	1016	.95	.90-1.01	1030	.96	.90-1.02
Lung cancer	330	**1.17**	**1.04-1.30**	249	1.01	.89-1.15

Relative risk of lung cancer by quantitative exposure to bitumen fume (15-yrs lag)



* relative risk adjusted for country, year, age and duration of employment

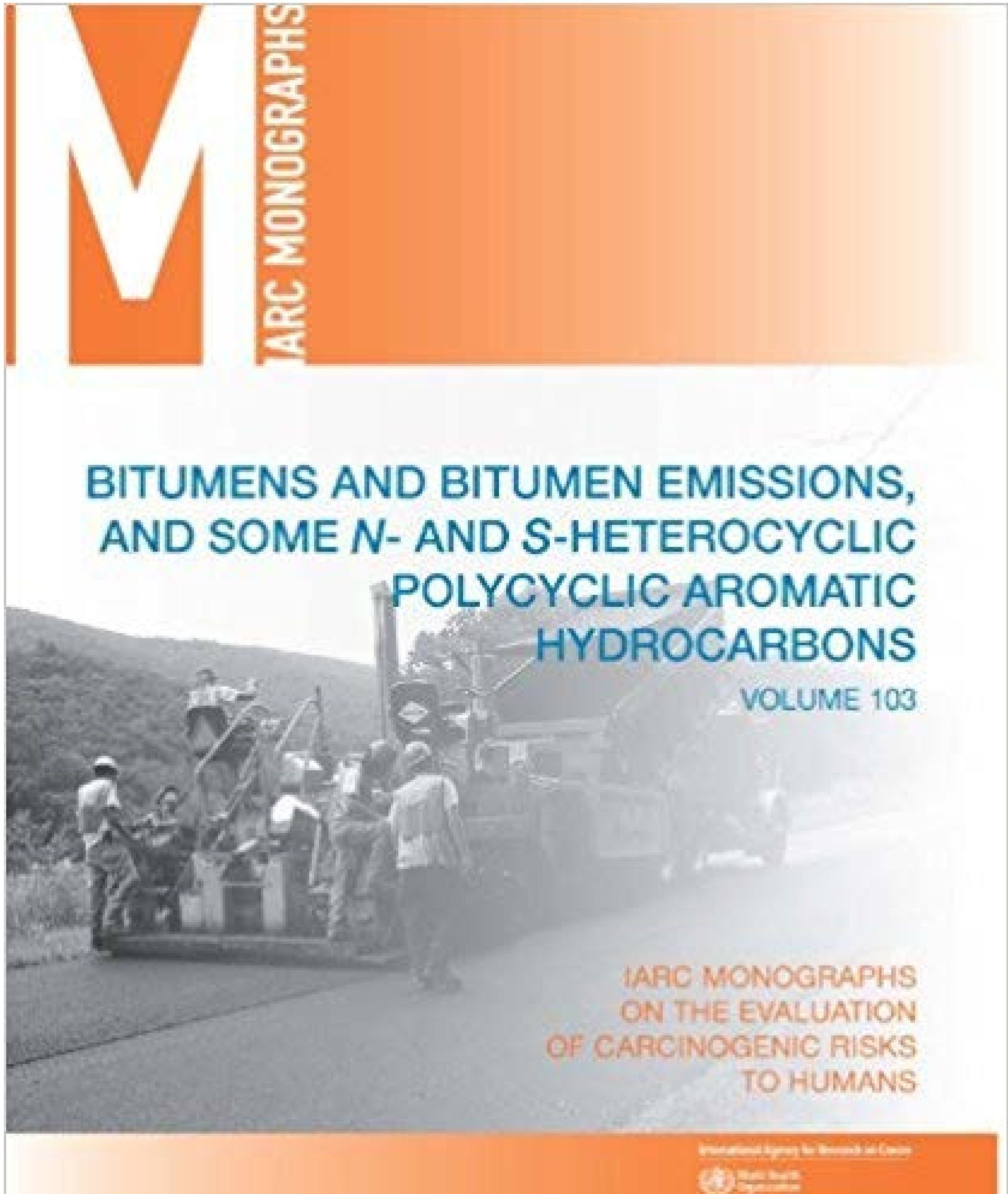
** p-value of test for linear trend

Confounding

- No data on tobacco smoking
  - but analyses in FIN, NOR and NL do not indicate that this is a big problem
  - also: increased SMRs for COPD, but not CVD
- Incomplete job histories: other occupational exposure to carcinogens?
- Incomplete adjustment for coal tar
- No data on dermal exposure

Discussion

- Did we learn more about lung cancer risk due to bitumen?
  - Yes, especially after the nested case-control study
  - Evidence coming from both cohort and ncc study resulted in bitumen be upgraded to IARC class 2B in 2013
- Power vs Quality tradeoff in occupational epidemiology -- a myth
- Quantitative exposure assessment was worth the trouble


IARC MONOGRAPHS
BITUMENS AND BITUMEN EMISSIONS, AND SOME N- AND S-HETEROCYCLIC POLYCYCLIC AROMATIC HYDROCARBONS
VOLUME 103
IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

Quantitative exposure assessment in community-based studies

SYNERGY

Pooled case-control studies

on lung cancer

example of Respirable Crystalline Silica

Background

- Historical measurements can be used for statistical modelling of workers' exposure levels
- For epi-studies mainly applied in industry-specific settings
- Quantitative exposure assessment in (multinational) community-based studies were non-existent
- ExpoSYN database contains (individual) measurement data from all over Europe and Canada, from all types of industries and occupations

Objectives

- Statistical modelling of RCS exposure data
- Elaboration of a quantitative job-exposure matrix (SYN-JEM) for community-based studies

Methods

Exposure measurement data

23,640 data points included

- *personal measurement*
- *quartz*
- *sampling duration 60-600 minutes*

<LOD (41%): single imputation assuming the same (log-normal) probability distribution as the observed data

Prior exposure level

- General population JEM: DOM-JEM
- Semi-quantitative scale: none-low-high

Methods – statistical model

$$Ln(Y) = \beta_0 + \beta_t T + \beta_s S + \beta_d D + \beta_i I_{dom} + b_{j1\text{-}428} J + b_{r1\text{-}7} Reg + \varepsilon$$

Where:

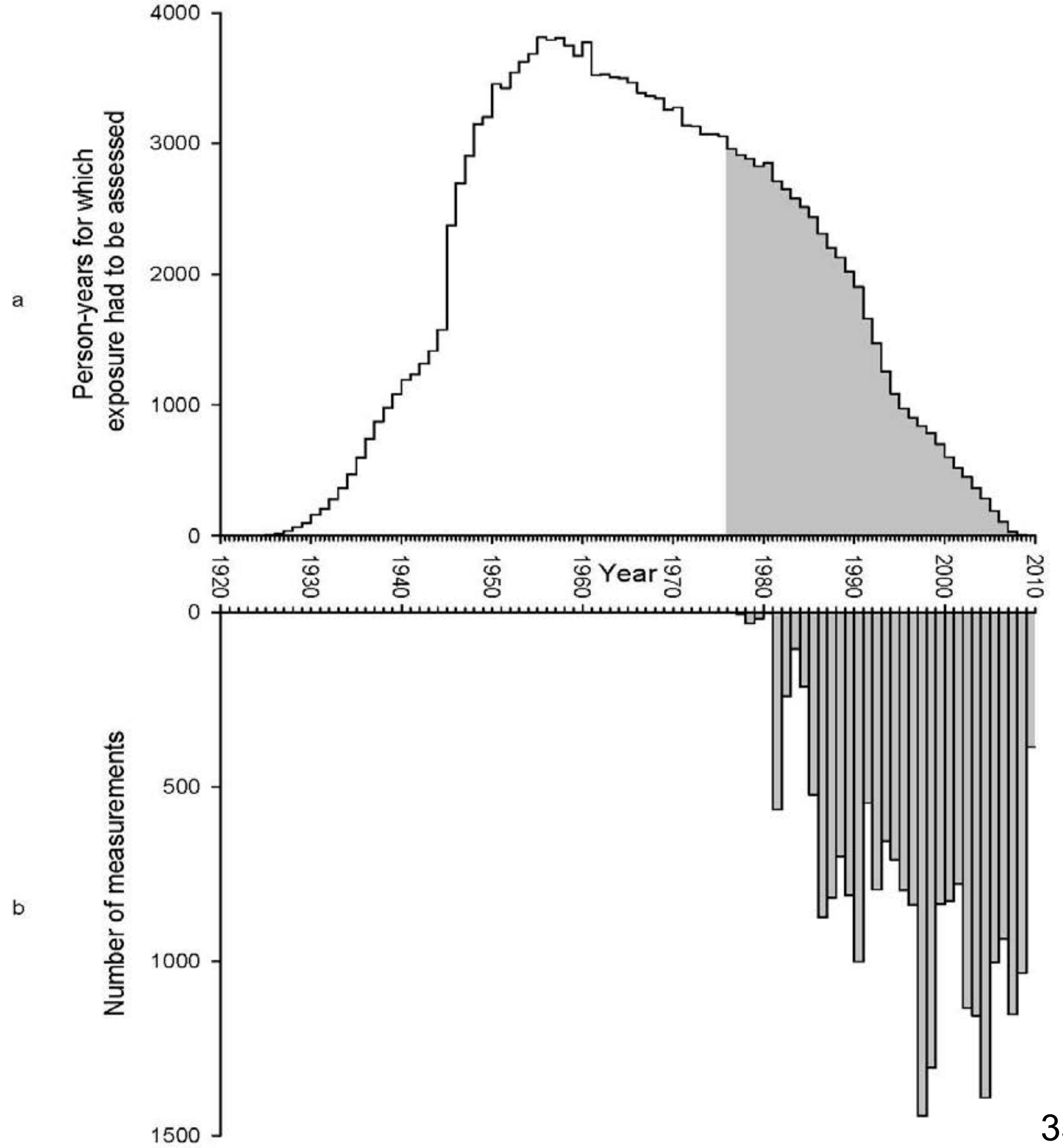
$Ln(Y)$	= natural log-transformed RCS concentration
β_0	= intercept
$\beta_t T$	= year of measurement *(ref. 1998)*
$\beta_s S$	= measurement strategy *(worst-case vs representative)*
$\beta_d D$	= sampling duration *(minutes)*
$\beta_i I_{dom}$	= DOM-JEM intensity rating
$b_{j1\text{-}428} J$	= random effect term job title
$b_{r1\text{-}7} Reg$	= random effect term region/country
ε	= residual error

Results

Model Parameters				
Categorical variables			**Number** (n=23,640)	**(%)**
Measurement strategy	Representative		19,864	(84%)
	Worst-case		3,776	(16%)
DOM-JEM score	Non-exposed		8,146	(34%)
	Low exposed		9,371	(40%)
	High exposed		6,123	(26%)
Region/country	Canada		2,384	(10%)
	France		4,995	(21%)
	Germany		8,419	(36%)
	Northern Europe		1,838	(8%)
	Southern Europe		373	(2%)
	UK		5,112	(22%)
	Western Europe		519	(2%)
Continuous variables		**Mean (±SD[a])**	**Median**	**Range**
Year of measurement	Years	1997 (7.6)	1998	1976-2009
Sampling duration	Minutes	273 (117)	290	60-600

[a] *SD=Standard Deviation*

Results


a
Person-years for which exposure had to be assessed
4000
3000
2000
1000
0
1920
1930
1940
1950
1960
Year
1970
1980
1990
2000
2010
b
Number of measurements
0
500
1000
1500

Results

Model Parameters /variance components				
Fixed effects terms			**GMR[a]**	**P-value**
Intercept	-		-	-
Year of measurement	Continuous - years		0.94	<.0001
Sampling duration	Continuous - minutes		0.998	<.0001
Measurement strategy	Representative (reference)		1.00	-
	Worst-case approach		1.77	<.0001
DOM-JEM score	High exposed (reference)		1.00	-
	Low exposed		0.61	0.004
	Non-exposed		0.63	0.004
Random effects terms			**GMR[a]**	**P-value**
Region/country	Canada		2.27	0.019
	France		0.61	0.104
	Germany		0.54	0.058
	Northern Europe		0.53	0.029
	Southern Europe		0.68	0.210
	UK		2.39	0.015
	Western Europe		1.52	0.165
Variance components		**Null model**	**Final model**	
		VC[b]	**VC[b]**	**%[c]**
Between jobs		0.87	0.71	18
Between regions		1.14	0.47	59
Residual		3.96	3.87	2

[a]GMR=Geometric Mean Ratio, calculated as exp(β); [b]variance; [c]% variance explained by fixed effects

Discussion – exposure model

Major strengths:

- model fully based on personal measurements
- many data points: 72% of exposed job titles covered

Observed time trend of -6% in line with previous studies

(*Creely et al. (2007):* -7% and -11% in various industries)

Bias in measurement data

→ measurements not random: biased towards circumstances where exposures occur

Most variance unexplained

→ between factory, between different jobs within the same ISCO code, between worker, and within worker variability

From model to SYN-JEM

Prediction model – SYN-JEM

$$Ln(Y) = ß_0 + ß_{jem\ score} + Random_{job} + Random_{region} + ß_{year} + (ß_{sampling\ duration} \times 480\ min)$$

- SYN-JEM consists of three axes: **job - region - year**
- Exposure levels are standardised to eight-hour shifts and a representative work situation

From model to SYN-JEM

Key decisions:

Override jobs considered non-exposed: 0 mg/m^3

Job estimates only applied when based on ≥5 data points

If not enough measurement data: estimates similar jobs *(with regard of job description and DOM-JEM score)*

Overall time trend for period from 1960 onwards; exposure ceiling for earlier years

Results

Cumulative RCS exposure (mg/m^3-years)

		Total population	Exposed	(%)	Median	10th-90th percentile
Total		37,959	9,423	(25%)	1.76	0.30-6.43
Region	Canada	3,890	470	(12%)	3.77	0.96-13.2
	CEE countries	5,293	1,164	(22%)	3.87	0.89-13.3
	France	7,146	1,632	(23%)	0.94	0.15-3.52
	Germany	8,435	3,350	(40%)	1.17	0.22-4.14
	Northern Europe	3,321	418	(13%)	2.29	0.39-6.61
	Southern Europe	8,266	2,156	(26%)	2.37	0.53-6.57
	UK	1,357	204	(15%)	2.75	0.79-13.2
	Western Europe	251	29	(12%)	3.46	0.89-8.59
Year of birth	1900-1909	23	1	(4%)	-	-
	1910-1919	2,410	602	(25%)	1.97	0.27-6.19
	1920-1929	10,213	3,156	(31%)	2.00	0.33-6.80
	1930-1939	12,479	3,319	(27%)	2.16	0.44-7.29
	1940-1949	8,152	1,551	(19%)	1.38	0.28-5.08
	1950-1959	3,489	597	(17%)	0.77	0.13-2.99
	1960-1969	1,044	185	(18%)	0.32	0.07-1.11
	1970-1979	139	12	(9%)	0.08	0.03-0.21
	1980-1989	10	0	(0%)	-	-

CEE countries=central and eastern European countries

Discussion SYN-JEM

Cumulative exposure levels calculated with SYN-JEM (median 1.76 mg/m^3-years among exposed) were comparable to levels reported in literature

- US granite workers median 0.72 mg/m^3-years (1924-1977) *(Attfield and Costello 2004*)

- 10 pooled studies: medians ranged from 0.13 mg/m^3-years for US industrial sand to 11.4 mg/m^3-years for Australian gold mines (*Steenland et al 2001)*

- German porcelain industry: median 0.56 mg/m^3-years (*Birk et al 2010*)

Discussion SYN-JEM

Cumulative exposure levels equally driven by exposure intensity and duration.

Correlations with cumulative exposure:

R=0.47 for average exposure level

R=0.56 for duration

Sensitivity analyses showed that exposure estimates were robust:

- cumulative exposure levels derived from SYN-JEM and alternative JEM specifications were overall highly correlated (R>0.90)
- somewhat lower when omitting region-specific estimate (R=0.80), or DOM-JEM prior (R=0.65)

Conclusion

Presented model enabled prediction of time-, job-, and region/country-specific exposure levels of RCS

SYN-JEM enabled estimation of lifetime exposure to RCS for individual subjects in the SYNERGY population

Construction of quantitative JEMs for community-based studies is an important methodological development to derive exposure-response relations between occupational exposures and health effects

Conclusion

Quantitative exposure assessment in multi-centric industrial cohort is possible and it is even possible in international community-based studies

It has resulted in improved evidence of carcinogenicity and has laid the foundation for quantitative risk analysis and better underpinning of occupational exposure limits

But without (access to) measurement data when can only guess

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