UMC Utrecht

Development of JEMs for quantitative exposure assessment

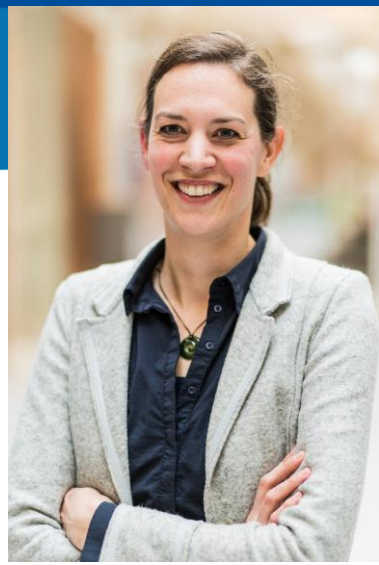
DOC*X
Danish
Occupational
Cohort

Dr Susan Peters

DOC*X research seminar, 22 November 2018

Universiteit Utrecht | INSTITUTE for RISK ASSESSMENT SCIENCES

University Medical Center Utrecht



Brief bio

Research focus: Exposure assessment science &
Chronic disease epidemiology
(cancer, neurodegenerative and respiratory disorders)

Current employment:
- Institute for Risk Assessment Sciences (IRAS), Utrecht University
- ALS centre, Neurology department, University Medical Centre Utrecht

2012: PhD from Utrecht University
Thesis: *" Quantitative exposure assessment in community-based studies"*

2012-2016: University of Western Australia

s.peters@uu.nl

Quantitative exposure assessment

Why do we want quantitative exposure assessment?

- Better proxy of delivered dose
- Exposure-response relationships
- Quantitative risk assessment (for legislation, health promotion)

Quantitative exposure assessment

Crystalline Silica

1986/87 Probable carcinogen (IARC Group 2a)
- limited evidence humans

International Agency for Research on Cancer

World Health Organization

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Quantitative exposure assessment

Crystalline Silica

1986/87 Probable carcinogen (IARC Group 2a)
- limited evidence humans

1997 & 2009 Human carcinogen (IARC Group 1)
- sufficient evidence humans

Primary focus on studies that employed quantitative data

Strongest evidence from pooled-analysis, supported by meta-analyses

Straif et al, Oncology 2009;10:453-4
Steenland et al, Cancer Causes Control 2001;12:773-84

Quantitative exposure assessment

International Agency for Research on Cancer

World Health Organization

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

March 2017: Welding

- Quantitative exposure assessment one of quality criteria epidemiological studies

November 2018: Update preamble

- Importance of evaluating exposure assessment quality in human studies

	Community-based studies	Industry-based studies
Starting point	Disease of interest.	Occupational exposure of interest.
Exposure assessment	Detailed exposure information is scarce, due to the wide range of workplaces. Exposure assessment is often qualitative (exposed/non-exposed) or semi-quantitative (non-/low/high exposed).	Detailed exposure information is often available, which enables high quality exposure assessment. Exposure measurement data can often be obtained for quantitative exposure assessment, which enables exploration of exposure-response relations.
Number of cases	Relatively high number of (exposed) cases.	Relatively low number of (exposed) cases. Particularly when studying a disease that is rare or has a long latency time, only a small part of the population under study will develop the disease of interest.
Occupational history	The full occupational history can be obtained, including all jobs ever performed by the subject.	Information is available on the work performed within the cohort (*i.e.* in that particular plant or industry).
Non-occupational information	Detailed (lifetime) information on potential confounders can be obtained from the subjects (*e.g.* smoking habits, medical history, and lifestyle).	No or only limited information is available on non-occupational confounders.
Generalisability	The subjects represent the general population, hence results are directly related to the general population.	The subjects represent the population from a specific industry. As not everybody has the same chance to be included in the cohort, results are not straightforwardly extrapolated to the general population.

Peters S. *Quantitative exposure assessment in community-based studies (2012)*

Quantitative EA in the general population

Teschke et al, 2002:

*"Incorporation of quantitative exposure measurements into case-control studies has always seemed a **quixotic goal**"*

But there are opportunities:

availability large national exposure databases → exposure modelling

Teschke et al. Occup Environ Med 2002;59:575-93

Quantitative EA in the general population

Challenges:

Availability of (good quality) data

- Coverage time periods and jobs
- Bias in measurement data

Assumptions inevitable

Absence of gold standard

Quantitative EA in the general population

Quantitative exposure assessment in community-based studies had not been published about till 2011/2012

Shanghai Women's Health Study

Friesen, et al. (2012): Benzene exposure in Chinese population

SYNERGY project

Peters, et al. (2011): Silica exposure in Europe/Canada

→ Using a combination of measurements and JEMs

SYNERGY project

Pooled analyses of 14 lung cancer case-control studies from Europe/Canada

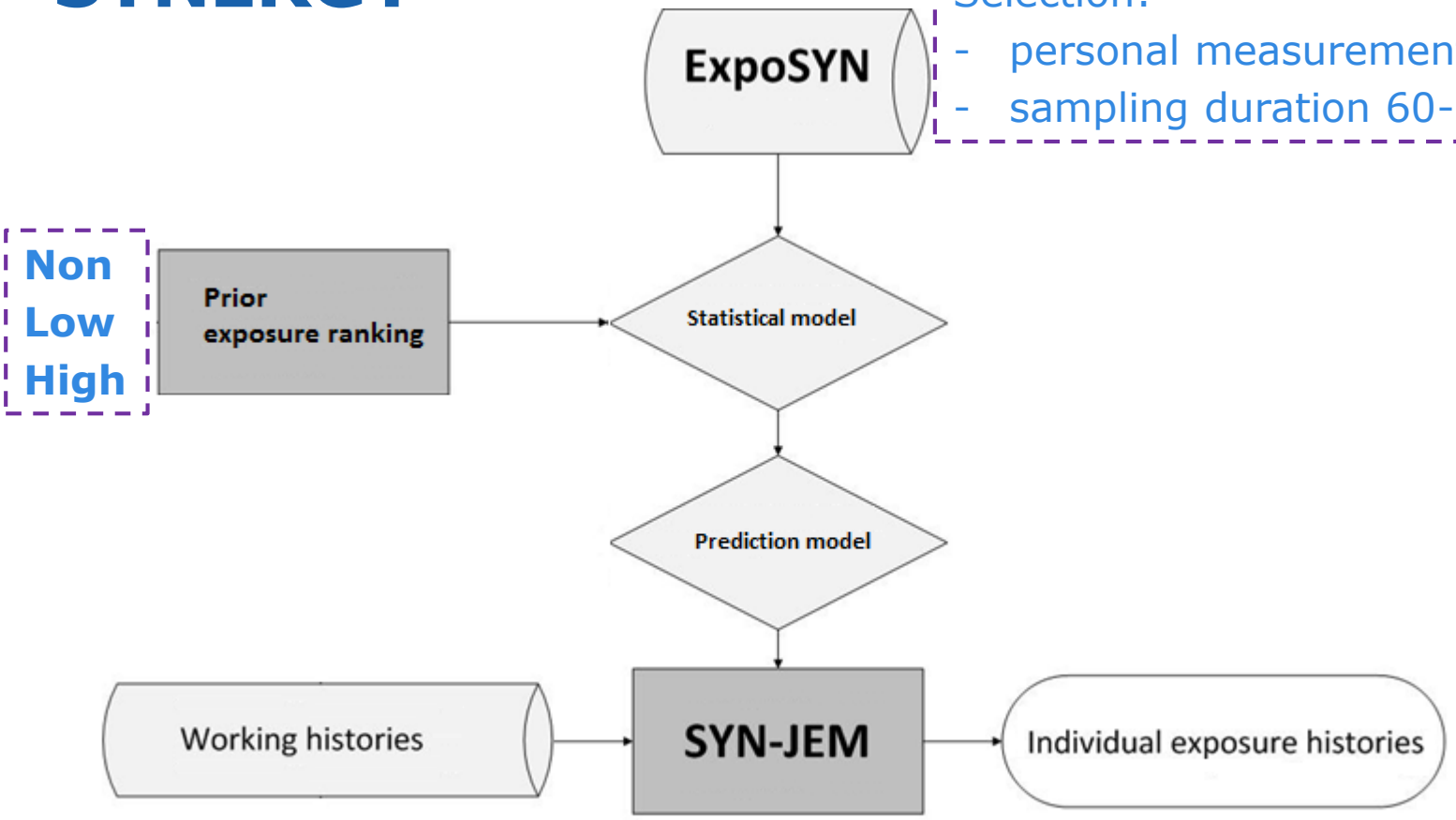
~18 000 cases

~22 000 controls

Job histories 1920s to 2010

SYNERGY

~360,000 measurements
Selection:
- personal measurements
- sampling duration 60-600min



SYNERGY – Exposure modelling

Exposure modelling is a working process rather than a standard procedure

Testing **if** and **how** to include each variable:

- Univariate testing
- Check correlations and consistency with literature
- Multivariate testing (random or fixed effect, grouping)
- Model fit

And also using expert knowledge!

SYNERGY – Exposure modelling

Mixed-effects model

Random effects:	job
	region
Fixed effects:	year of measurement
	sampling duration (minutes)
	prior exposure ranking (DOM-JEM)
	measurement strategy

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

Exposure modelling – silica example

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

Exposure modelling – silica example

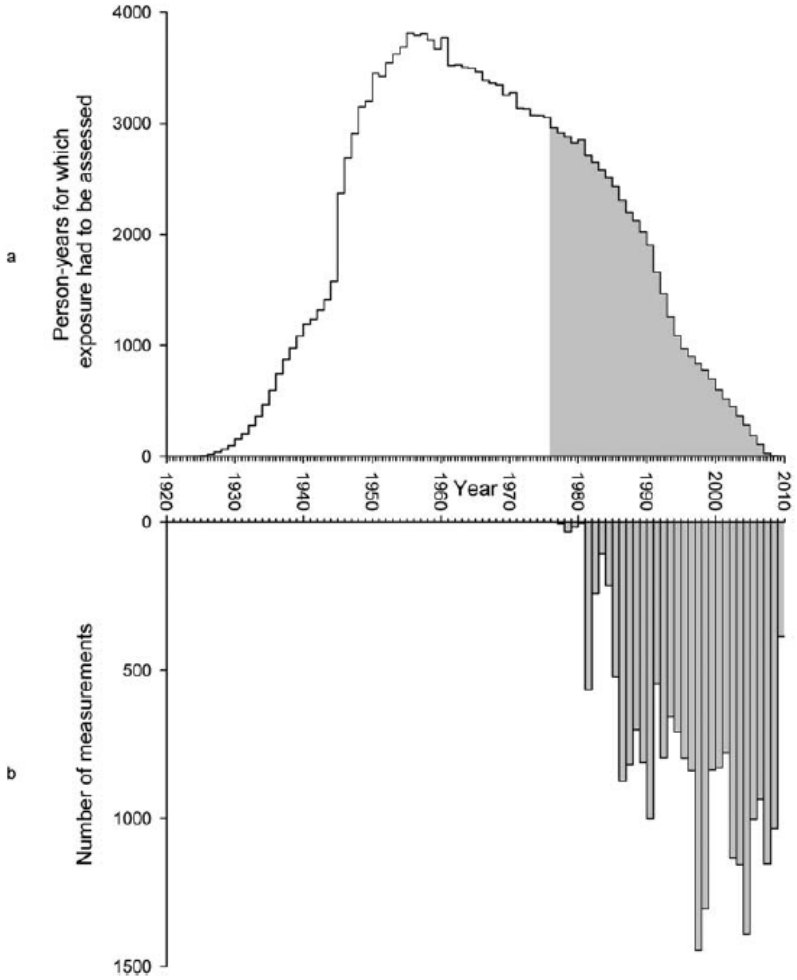


Table 2 Fixed and random effects model parameters plus variance components from the mixed-effects model for personal RCS exposure measurements (n = 23,640)

Model Parameters/variance components					
Fixed effects terms		β[a]	SE[b]	GMR[c]	*P*-value
Intercept	—	−2.96	0.30	—	—
Year of measurement	Continuous - years	−0.06	0.003	0.94	<.0001
Sampling duration	Continuous - minutes	−0.002	0.0002	0.998	<.0001
Measurement strategy	Representative	Ref.	-	1.00	-
	Worst-case approach	0.57	0.06	1.77	<.0001
DOM-JEM score	High exposed	Ref.	-	1.00	-
	Low exposed	−0.49	0.17	0.61	0.004
	Non-exposed	−0.47	0.16	0.63	0.004
Random effects terms		BLUP[d]	SE[b]	GMR[c]	*P*-value
Region/country	Canada	0.82	0.27	2.27	0.019
	France	−0.50	0.26	0.61	0.104
	Germany	−0.61	0.26	0.54	0.058
	Northern Europe	−0.63	0.26	0.53	0.029
	Southern Europe	−0.38	0.28	0.68	0.210
	UK	0.87	0.26	2.39	0.015
	Western Europe	0.42	0.27	1.52	0.165

	Null model		Final model		
Variance components	VC[e]	SE[b]	VC[f]	SE[b]	%[g]
Between jobs	0.87	0.09	0.71	0.08	18
Between regions	1.14	0.66	0.47	0.27	59
Residual	3.96	0.04	3.87	0.04	2

[a] β for fixed effects derived from the mixed-effects model based on restricted maximum likelihood method. [b] SE = Standard Error. [c] GMR = Geometric Mean Ratio, calculated as exp(β). [d] BLUP = Best Linear Unbiased Predictor for random effects, derived from the mixed-effects model. [e] variance from model with only random effects. [f] variance from model with fixed and random effects. [g] percentage of variance explained by fixed effects.

Exposure modelling – silica example

Job-exposure matrices

Low cost (once developed!)
Standardized assessment within and between studies
Avoiding recall bias

Assumes homogeneity of exposure within groups

Exposure modelling – silica example

	RCS
Number of measurements	23,640
Time trend (% per year)	-6%
Decrease concentration per hour increase in sampling duration	-9%
Low vs High (GMR*)	0.61
Fold range 10^{th}-90^{th} percentile exposed job estimates	5.03

*GMR=geometric mean ratio

Exposure modelling – silica example

In addition to the statistical model, there is a prediction model:

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

SYN-JEM consists of three axes: **job – region - year**

Exposure levels are standardised to 8-hour shifts and a representative work situation

Exposure modelling – silica example

WORKERS ≠ MEASUREMENTS

Exposure modelling – silica example

Key decisions:

1. Override jobs considered non-exposed
2. Job estimates only applied when based on ≥5 data points; if not enough, estimate based on calibrated prior ranking
3. Overall time trend for period with measurement data (1960 onwards); exposure ceiling for earlier years

Peters S, et al. *Sensitivity analyses of exposure estimates from a quantitative job-exposure matrix (SYN-JEM) for use in community-based studies.* Annals of Occupational Hygiene (2013) 57(1):98-106

Silica in general population

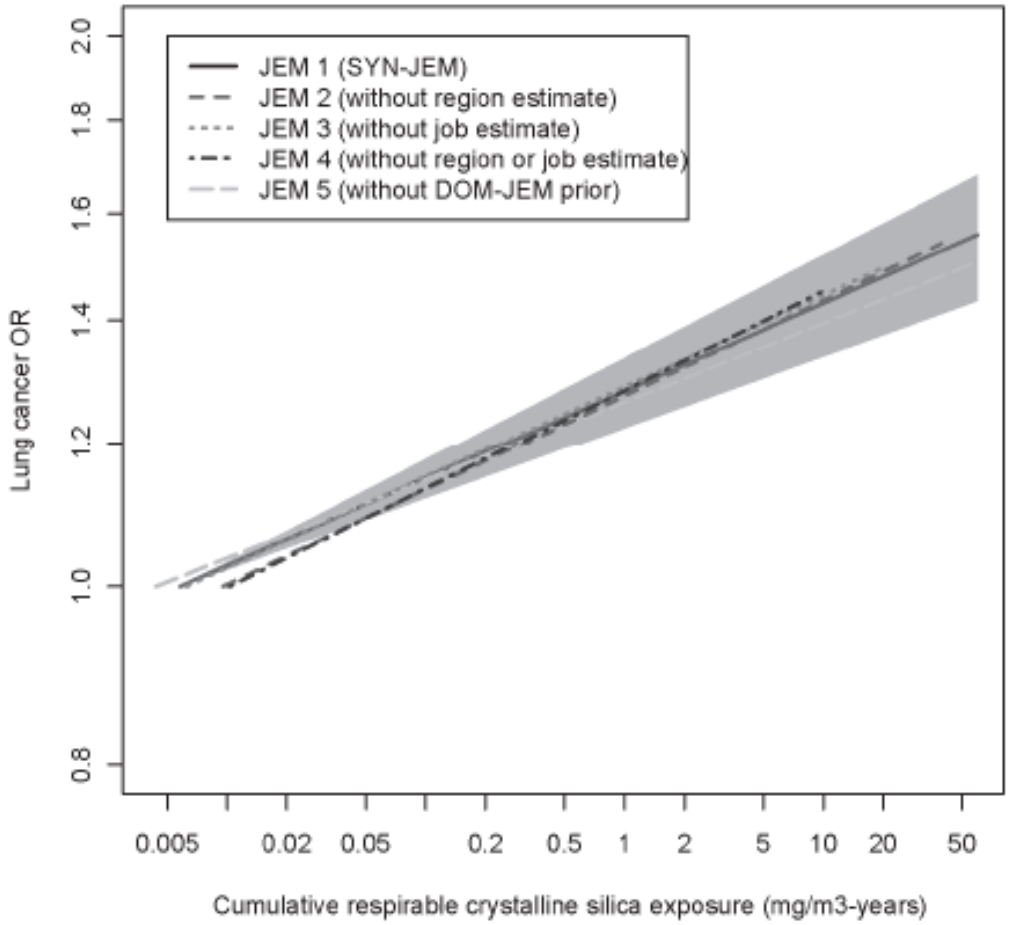
Table 3. Comparison of cumulative exposure levels to RCS (mg/m^3-years) within the SYNERGY population based on SYN-JEM and alternative models.

		Pearson correlation		Cumulative exposure level (mg/m^3-years RCS)		
		All subjects (n = 37 959)	Exposed (n = 9423)	Mean	Median (difference to SYN-JEM)	10th–90th percentile
SYN-JEM		1.00	1.00	2.86	1.76	0.30–6.43
Alternative models						
A	No region-specific estimate	0.80	0.67	3.35	2.17 (+23%)	0.41–7.93
B	No requirement ≥5 measurements	0.99	0.99	2.81	1.69 (–4%)	0.29–6.34
C	Common mean for job code without data	0.98	0.97	2.84	1.76 (+0%)	0.29–6.38
D	No job-specific estimate	0.91	0.86	2.20	1.46 (–17%)	0.26–4.58
E	No region- or job-specific estimate	0.74	0.58	2.52	1.83 (+4%)	0.41–5.80
F	Time trend: exposure ceiling before 1950	0.99	0.98	3.60	2.27 (+29%)	0.39–8.11
G	Time trend: exposure ceiling before 1970	0.99	0.99	2.02	1.18 (–33%)	0.19–4.54
H	Time trend: peak at 1960	0.99	0.98	2.32	1.31 (–26%)	0.18–5.34
I	No DOM-JEM prior in statistical model[a]	0.65	0.63	2.59	1.41 (–20%)	0.28–6.18

[a]10 938 subjects were considered exposed with alternative I.

Peters S, et al. Annals of Occupational Hygiene (2013) 57(1):98-106

Exposure modelling – silica example



Peters S. *Quantitative exposure assessment in community-based studies (2012)*

Exposure modelling

Many issues to deal with during modelling process:

- Imputation of values <LOD (and test its effect)
- Model industry: 4-, 3-, 2-digit or in categories?
- Use a prior? E.g. non – low – high exposed
- Country effect: in multivariate model significant, but no clear trend. Regions might be better? Interactions?
- What time trend?
- Check correlations
- Distribution sampling time: difference task based / full shift measurements?
- Personal vs stationary measurements
- What reference categories to use?

… many more will show up during the modelling process

Exposure modelling

Random effect: Mean predicted exposure for variable X with few measurements gets "shrunk" towards the (country- and job-specific etc..) "common" mean

Lower mean squared error (MSE) a.k.a. borrowing strength

Results in biased estimation if this "common" mean does not exist

Exposure modelling

Using mixed-effects models, we combined measurement data with prior exposure ranking (non-low-high)

If limited number of measurements available:

→ Calibrated prior + time trend

Exposure modelling

Are measurements really objective?

Situations/workplaces with higher-intensity exposure more likely to be monitored

- probably more prominent in low-exposed jobs

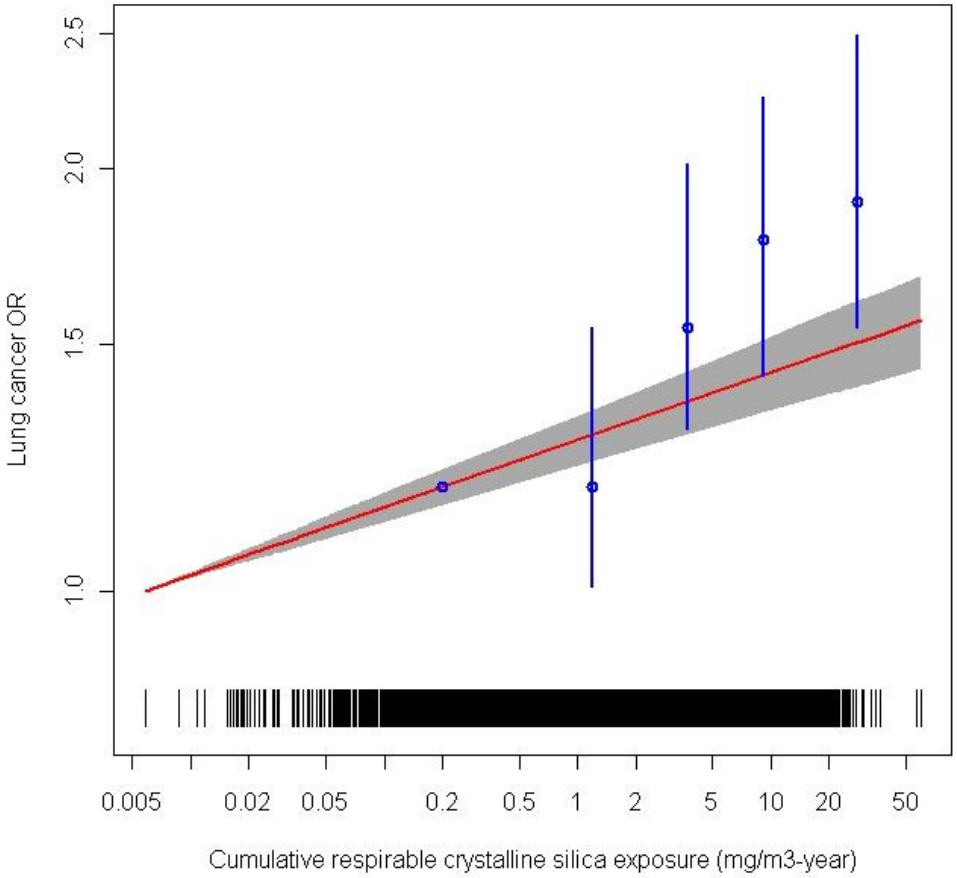
- contrast in estimated GM for prior ranking was lower than expected and probably underestimated in our model

Exposure modelling

"SYN-JEM" enabled quantitative estimation of lifetime exposure to occupational carcinogens for individual subjects in a large community-based study

→ derivation quantitative exposure-response relations between occupational exposures and health effects

Silica exposure in general population



Risk for each twofold increase in cumulative RCS exposure:

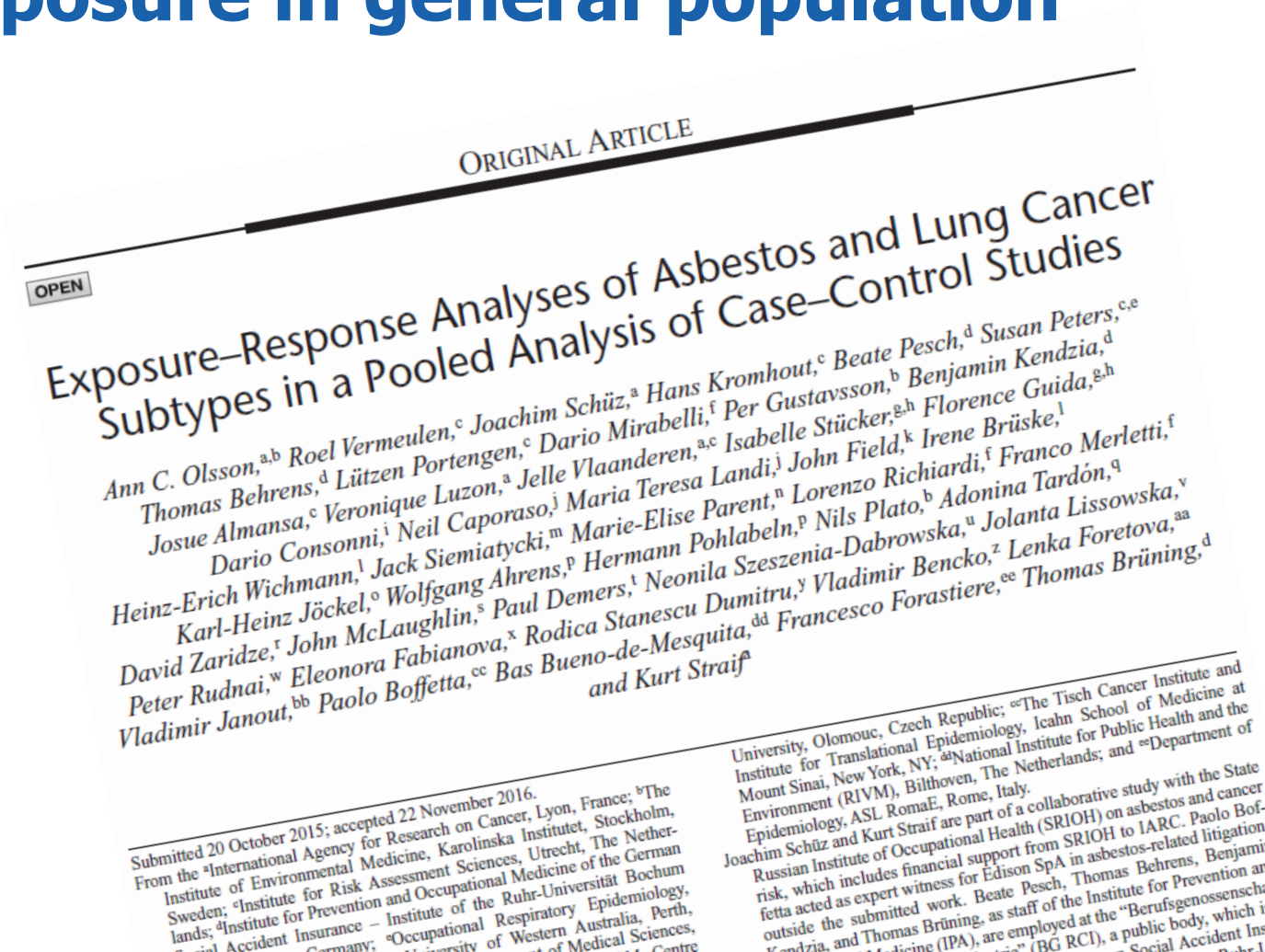
SYN-JEM: 1.034
(95%CI 1.027-1.041)

Steenland: 1.048
(95%CI 1.025-1.071)

Peters S. Quantitative exposure assessment in community-based studies (2012)
Steenland et al, Cancer Causes Control 2001;12:773-84

Asbestos
~~Silica~~ exposure in general population

Developed framework can be adapted to other exposures



ORIGINAL ARTICLE

OPEN

Exposure–Response Analyses of Asbestos and Lung Cancer Subtypes in a Pooled Analysis of Case–Control Studies

Ann C. Olsson,[a,b] Roel Vermeulen,[c] Joachim Schüz,[a] Hans Kromhout,[c] Beate Pesch,[d] Susan Peters,[c,e] Thomas Behrens,[d] Lützen Portengen,[c] Dario Mirabelli,[f] Per Gustavsson,[b] Benjamin Kendzia,[d] Josue Almansa,[c] Veronique Luzon,[a] Jelle Vlaanderen,[a,c] Isabelle Stücker,[g,h] Florence Guida,[g,h] Dario Consonni,[i] Neil Caporaso,[j] Maria Teresa Landi,[j] John Field,[k] Irene Brüske,[l] Heinz-Erich Wichmann,[l] Jack Siemiatycki,[m] Marie-Elise Parent,[n] Lorenzo Richiardi,[f] Franco Merletti,[f] Karl-Heinz Jöckel,[o] Wolfgang Ahrens,[p] Hermann Pohlabeln,[p] Nils Plato,[b] Adonina Tardón,[q] David Zaridze,[r] John McLaughlin,[s] Paul Demers,[t] Neonila Szeszenia-Dabrowska,[u] Jolanta Lissowska,[v] Peter Rudnai,[w] Eleonora Fabianova,[x] Rodica Stanescu Dumitru,[y] Vladimir Bencko,[z] Lenka Foretova,[aa] Vladimir Janout,[bb] Paolo Boffetta,[cc] Bas Bueno-de-Mesquita,[dd] Francesco Forastiere,[ee] Thomas Brüning,[d] and Kurt Straif[a]

Submitted 20 October 2015; accepted 22 November 2016.

From the [a]International Agency for Research on Cancer, Lyon, France; [b]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [c]Institute for Risk Assessment Sciences, Utrecht, The Netherlands; [d]Institute for Prevention and Occupational Medicine of the German Accident Insurance – Institute of the Ruhr-Universität Bochum [e]Occupational Respiratory Epidemiology, University of Western Australia, Perth, University, Olomouc, Czech Republic; [cc]The Tisch Cancer Institute and Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, NY; [dd]National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; and [ee]Department of Epidemiology, ASL RomaE, Rome, Italy.

Joachim Schüz and Kurt Straif are part of a collaborative study with the State Russian Institute of Occupational Health (SRIOH) on asbestos and cancer risk, which includes financial support from SRIOH to IARC. Paolo Boffetta acted as expert witness for Edison SpA in asbestos-related litigation outside the submitted work. Beate Pesch, Thomas Behrens, Benjamin Kendzia, and Thomas Brüning, as staff of the Institute for Prevention and Medicine (IPA), are employed at the "Berufsgenossenschaftliches" (BG RCI), a public body, which is

Exposure modelling

The strength of exposure modelling is that one can create an objective quantitative measure of exposure.

Not all jobs, countries and time periods are covered by exposure data:

- algorithm (based on these data) can assign estimates to all possible combinations
- estimates in all countries/studies are comparable

SYNERGY project

Ann. Occup. Hyg., 2016, Vol. 60, No. 7, 795–811
doi:10.1093/annhyg/mew034
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BOHS
The Chartered Society for Worker Health Protection

SYN-JEM: A Quantitative Job-Exposure Matrix for Five Lung Carcinogens

Susan Peters[1,2*], Roel Vermeulen[1,3], Lützen Portengen[1], Ann Olsson[4], Benjamin Kendzia[5], Raymond Vincent[6], Barbara Savary[6], Jérôme Lavoué[7], Domenico Cavallo[8], Andrea Cattaneo[8], Dario Mirabelli[9], Nils Plato[10], Joelle Fevotte[11], Beate Pesch[5], Thomas Brüning[5], Kurt Straif[4] and Hans Kromhout[1]

1.Environmental Epidemiology Division, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands;
2.Occupational Respiratory Epidemiology, School of Population Health, University of Western Australia, Perth, Australia;
3.Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands;
4.International Agency for Research on Cancer, Lyon, France;
5.Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-Universität Bochum, Bochum, Germany;
6.Institut National de Recherche et de Sécurité, Vandoeuvre lès Nancy, France;
7.Research Centre of University of Montreal Hospital Research Centre, Canada;
8.Department of Science and High Technology, Università degli Studi dell'Insubria, Como, Italy;
9.Cancer Epidemiology Unit, CPO-Piemonte and University of Turin, Turin, Italy;
10.The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden;
11.Département santé travail, Institut de veille sanitaire, St Maurice, France
*Author to whom correspondence should be addressed. Tel: +31-30-253-9440; fax: +31-30-253-9499; e-mail: h.kromhout@uu.nl
Submitted 20 October 2015; revised 20 April 2016; revised version accepted 12 May 2016.

ABSTRACT

Objective: The use of measurement data in occupational exposure assessment allows more quantitative analyses of possible exposure–response relations. We describe a quantitative exposure assessment approach for five lung carcinogens (i.e. asbestos, chromium-VI, nickel, polycyclic aromatic hydrocarbons (by its proxy benzo(a)pyrene (BaP)) and respirable crystalline silica). A quantitative job-

Proof of concept

Opportunities for:

- Studying interactions
- Subgroups analyses

  (*e.g.* lung cancer subtypes, women, non-smokers)

But also:

- to study potential associations with other diseases using case-control studies

Take home messages

Good quality and quantitative exposure assessment highly important in epi studies

Exposure modelling enables quantitative exposure assessment at individual level, without measuring each subject

An algorithm (or quantitative JEM) can assign estimates to all possible combinations (job title*region*year) in the general population

But also keep in mind:

- Large amounts of data are needed to develop such a JEM
- A quantitative JEM will still have the same limitation of assuming homogeneity within jobs
- Exposure modelling requires many assumptions
- Measurement data are not fully objective either

Thank you!