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

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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-exposure matrix (JEM) was developed based on statistical modeling of large quantities of personal measurements.

Methods: Empirical linear models were developed using personal occupational exposure measurements (n = 102 306) from Europe and Canada, as well as auxiliary information like job (industry), year of sampling, region, an *a priori* exposure rating of each job (none, low, and high exposed), sampling and analytical methods, and sampling duration. The model outcomes were used to create a JEM with a quantitative estimate of the level of exposure by job, year, and region.

Results: Decreasing time trends were observed for all agents between the 1970s and 2009, ranging from −1.2% per year for personal BaP and nickel exposures to −10.7% for asbestos (in the time period before an asbestos ban was implemented). Regional differences in exposure concentrations (adjusted

for measured jobs, years of measurement, and sampling method and duration) varied by agent, ranging from a factor 3.3 for chromium-VI up to a factor 10.5 for asbestos.
Conclusion: We estimated time-, job-, and region-specific exposure levels for four (asbestos, chromium-VI, nickel, and RCS) out of five considered lung carcinogens. Through statistical modeling of large amounts of personal occupational exposure measurement data we were able to derive a quantitative JEM to be used in community-based studies.

KEYWORDS: asbestos exposure; chromium; exposure assessment—mixed models; exposure assessment; nickel; polycyclic aromatic hydrocarbons; retrospective exposure assessment; respirable crystalline silica

INTRODUCTION

Industry-based cohort studies are frequently used to investigate associations between occupational exposures and disease outcomes. Detailed information about the subjects' job and specific tasks, combined with exposure measurements, generally result in high-quality quantitative exposure estimates in those studies (Kauppinen 1994; Checkoway *et al.*, 2004). However, when the disease under study is rare, community-based case-control studies are a necessity. The wider range of jobs, industries, and companies in community-based studies complicates detailed exposure assessment. Consequently, assessment is often done in a qualitative or semi-quantitative way (Teschke *et al.*, 2002). Alternatively, quantitative exposure assessment in community-based studies increases the potential to investigate exposure time–response associations in addition to specific industrial settings with often higher (cumulative) exposures (Richardson *et al.*, 2012; Vermeulen and Chadeau-Hyam, 2012).

Recently, a framework was developed to improve exposure assessment in community-based studies by integrating quantitative measurement data with prior occupational hygiene knowledge. This framework, which was based on earlier work by Wild (2002) and Friesen *et al.* (2012), has been published for respirable crystalline silica (RCS) in a series of papers (Peters *et al.*, 2011, 2012, 2013). Individual measurements of occupational exposures from Europe and Canada were collected in a central database (i.e. ExpoSYN, Peters *et al.*, 2012) following a structured format. Variation in exposure levels according to region/country, job, and calendar year was assessed by applying linear mixed-effects models. *A priori* ratings were obtained from an independently developed job-exposure matrix (JEM) where each job was classified as non-, low or high exposed (Peters *et al.*, 2011a; Peters *et al.*, 2011b). This approach demonstrated that meaningful exposure estimates could be discerned, which varied over time and by region and jobs, resulting in more contrast in exposure estimates as compared to a JEM with a semi-quantitative character. Subsequently, sensitivity analyses of model parameterizations (including changes in the application of job- and region-specific estimates and time trend, and omitting the *a priori* exposure rating) showed that the approach was robust for different assumptions made (Peters *et al.*, 2013).

We here describe the additional modeling and elaboration of SYN-JEM for asbestos, chromium-VI, nickel, and polycyclic aromatic hydrocarbons (PAH). This paper focuses on the comparison of the driving factors in these models and the agent-specific particularities of SYN-JEM. Our objective was to examine the feasibility of quantitative exposure assessment for a range of agents in community-based studies.

METHODS

Personal measurements from the ExpoSYN database (Peters *et al.*, 2012), covering the 1970s until 2009, were selected for modeling when a job code was available and the sampling duration was between 60 and 600 min. This selection resulted in 27 958 measurements for asbestos, 24 150 for chromium (including 8363 measurements for chromium-VI), 22 081 for nickel, 4477 for benzo(a)pyrene (BaP) as proxy for PAH, and 23 640 for RCS (Table 1). Empirical models were developed based on those measurements.

Basic framework for statistical model

The basic statistical model was a linear mixed-effects model, using the same structure for all five agents. Random effects terms included region/country and job title, for which best linear unbiased predictors (BLUP) were derived. Where measurements were

Table 1. Overview of exposure assessment approach for the lung carcinogens selected for the SYNERGY project

Agent	Personal measurement data			Statistical model			Elaboration of SYN-JEM	
	N	% <LOD	Time period covered	Random effects terms in model	Fixed effects terms in model	Categories fixed effects	Unit of exposure	Year of maximum level
Asbestos[a]	27 958	32%	1971–2009	Job title Region	Year of measurement Sampling duration Prior exposure rating Asbestos ban Years since ban implementation	Continuous Continuous Non or low versus high Period with ban versus period without ban continuous (0 for years before ban)	f ml^{-1}	1975
Chromium-VI[b,c]	24 150	35%	1977–2009	Job title Region	Year of measurement Sampling duration Prior exposure rating Measurement strategy Analytical method Chromium type	Continuous Continuous Non or low versus high Worst-case versus representative AAS, X-ray, or photometry versus ICP CR-VI/total CR	mg m^{-3}	1970
Nickel[b,d]	22 081	28%	1977–2009	Job title Region	Year of measurement Sampling duration Prior exposure rating Measurement strategy Analytical method	Continuous Continuous Non or low versus high Worst-case versus representative AAS or X-ray versus ICP	mg m^{-3}	1970

Table 1. *Continued*

Agent	Personal measurement data			Statistical model			Elaboration of SYN-JEM	
	N	% <LOD	Time period covered	Random effects terms in model	Fixed effects terms in model	Categories fixed effects	Unit of exposure	Year of maximum level
BaP[b,e]	4477	49%	1975–2009	Job title Region	Year of measurement Sampling duration Prior exposure rating Measurement strategy Analytical method	Continuous Continuous Non or low versus high Worst-case versus representative Gas or unspecified chromatography versus HPLC	$\mu g/m^3$	1975
RCS	23 640	37%	1976–2009	Job title Region	Year of measurement Sampling duration Prior exposure rating Measurement strategy	Continuous Continuous Non or low versus high Worst-case versus representative	$mg\ m^{-3}$	1960

[a]No asbestos exposure assigned before 1945 in the Central and Eastern European countries, France, Germany, the Netherlands, Spain, and Sweden.
[b]Conversion factor applied to inhalable sampler.
[c]Measurements of both chromium-VI ($n = 8.363$; 35%) and total chromium ($n = 15.787$; 65%) were included.
[d]Nickel measurements were only included when total nickel compounds were determined.
[e]Measurements of benzo(a)pyrene (BaP) in the particulate phase were selected to represent polycyclic aromatic hydrocarbons (PAH).
LOD, limit of detection.

scarce and/or highly variable, these BLUPs shrunk the job- and region-specific estimates towards their respective overall mean and the job-specific estimates to the mean within each prior exposure rating category, assuming that estimates are normally distributed with a mean value of 0 (Friesen *et al.*, 2012). Prior exposure rating, measurement year, and sampling duration were included as fixed effects. The prior exposure rating was derived from a general population JEM (DOM-JEM), assigning no, low, or high exposure levels to all job titles listed in ISCO-68 (Peters *et al.*, 2011a). Some modifications were made to DOM-JEM for the ratings for asbestos, PAH, and RCS. The rating was changed from 'no' to 'low' exposure if the individual was employed in a particular industry where exposure was likely (Supplementary Table S1).

Because of limited number of measurements in some countries, the following *a priori* categorization based on geographic proximity of region/country was made: Canada; Central and Eastern European (CEE) countries; France; Germany; Italy/Spain; Sweden (including data from all Nordic countries); the United Kingdom (UK); and the Netherlands. Supplementary Table S2 shows the number of agent-specific measurements included from each region.

The linear mixed-effects models were developed using the 'Proc Mixed' restricted maximum likelihood method in SAS v9.2 (SAS Institute Inc. Cary, NC, USA).

Agent-specific aspects

Starting with the basic framework, additional fixed effects were selected for adjustment for each agent (Table 1) in order to make best use of the available data. Selection was based on a statistical significant effect of these additional variables in the model ($P < 0.05$) and whether the observed effect was in the expected direction, based on literature and industrial hygiene knowledge. Variables that were excluded after consideration were: 'measurement reason' from each of the models (due to collinearity with measurement strategy), and 'analytical method' from the asbestos model (collinearity with region) and RCS model (because the choice of method was dependent on expected concentration).

Asbestos measurements were only included when fibre counts were available (either analyzed by electron microscopy (EM) or phase contrast microscopy (PCM)). Overall, PCM was used in >95% of samples, except for the German asbestos measurements where >99% were analyzed with EM. These two analytical methods might result in different estimates of fibre counts, but there is no consensus on a universal conversion factor. With 'analytical method' in the model, however, the comparison of EM with PCM would be confounded by differences in exposure between Germany and the UK (country contributing the majority of asbestos data). We therefore did not adjust for analytical method in the asbestos model.

Asbestos consumption in Europe became only widespread following World War II (Virta, 2006) and exposure was therefore not assigned before 1945. Exceptions were Italy, Russia, and Canada due to asbestos mining, and the UK where asbestos consumption started earlier (Hodgson *et al.*, 2005; Virta, 2006). Most western countries have banned the use of asbestos completely in the last decades of the twentieth century. The country-specific year of the implementation of the asbestos ban (Supplementary Table S3) was added to the model as a fixed effect, indicating whether the measurement represented the period before or after the ban. Asbestos bans have often been introduced stepwise and we applied the year of the complete ban. For example, the use, machining, and processing of asbestos in Sweden was prohibited in 1982, but there were still some exceptions until 1986 (Järvholm *et al.*, 1999). The decrease in exposure level preceding the complete ban has been captured in the model with a linear time trend.

For the chromium-VI model, we included measurements of both chromium-VI ($n = 8363$) and total chromium ($n = 15\,787$) to increase the number of data points and thus coverage of jobs, regions, and time periods. The variable 'chromium type' was subsequently included as a fixed effect resulting in all estimates being standardized to chromium-VI levels.

Field trials in the European CALTOOL project indicated that the performance of inhalable dust samplers is variable (Mark *et al.*, 2015). Fixed conversion factors (Supplementary Table S4) were applied accordingly to the chromium, nickel, and BaP measurements for which the inhalable fraction was sampled with different sampling heads. Models for chromium-VI and nickel were additionally adjusted for analytical method.

For measurements below the limit of detection (LOD), we applied a single imputation using maximum

likelihood estimation (Lubin *et al.*, 2004), assuming that these measurements follow the same log-normal probability distribution as the observed data. The non-detected value was substituted with a random draw between 0 and the measurement-specific LOD. Percentages of measurements below LOD were 32, 35, 28, 49, and 37% for asbestos, chromium, nickel, BaP, and RCS, respectively (Table 1). Analyses using multiple imputation draws indicated that results did not alter.

Quantitative SYN-JEM

The mixed-effects model resulted in parameter estimates for *a priori* exposure rating, job title, region, year, and sampling duration. The latter was applied to model the exposure level for an eight-hour workshift (480 min). The average sampling duration ranged from 178 min for asbestos to 301 min for BaP. All estimates were standardized to a representative measurement strategy except for asbestos where the strategy was unknown for two-thirds of the measurements.

The expression used for the predictions in the quantitative SYN-JEM was:

$$\begin{aligned} \boldsymbol{Ln(Y)} = {} & \text{Intercept} + \boldsymbol{\beta}_{\text{prior rating}} + \text{Random}_{\text{job}} \\ & + \text{Random}_{\text{region}} + \boldsymbol{\beta}_{\text{year}} \\ & + \boldsymbol{\beta}_{\text{sampling duration}} \times 480 \text{ minutes} \\ & + \left(\begin{array}{l} \boldsymbol{\beta}_{\text{measurement strategy}} + \boldsymbol{\beta}_{\text{analytical method}} \\ + \boldsymbol{\beta}_{\text{type of chromium}} + \boldsymbol{\beta}_{\text{asbestos ban}} \end{array} \right) \end{aligned}$$

with in bold the basic model for all exposures and between parenthesis additional factors used for specific agents.

The exponent of the natural log-transformed exposure level (ln(Y)) provides an annual geometric mean (GM) exposure level to any of the five agents for a given job, region, and year. These model predictions formed the basis to develop SYN-JEM. The main steps involved in this process are described below. Asbestos was expressed as f ml^{-1}; chromium-VI, nickel and RCS as mg m^{-3}; and BaP as µg m^{-3}.

In our models we estimated an agent-specific overall linear time trend, i.e. we applied the same trend to all jobs and regions. Temporal changes in exposure levels were explored using splines; visual inspection suggested that a log-linear trend was the most appropriate. The inclusion of the year of ban in the asbestos model allowed for different time trends before and after the ban. We have previously shown that working years in the SYNERGY population and exposure measurement data overlap for about one third (Peters *et al.*, 2011), requiring back extrapolation of more recent data to the earlier years. A constant maximum exposure level was applied for the earlier years to avoid assigning unrealistic levels to jobs held in the beginning of the 20th century, as would happen when fully back extrapolating the observed time trend from more recent years. The agent-specific maximum level was the level assigned to a job-region combination in a designated year for each agent (Table 1), before which insufficient numbers of measurements were available to estimate a reliable time trend. Sensitivity analyses showed that modification of the time trend for RCS (namely maximum levels based on estimates for 10 years earlier or later) did not alter the relative ranking of the exposure of cases and controls (R_P = 0.99) (Peters *et al.*, 2013).

We aimed at assessing exposure levels for each job title listed in ISCO-68. Jobs classified as exposed by DOM-JEM and with exposure measurements available, were assigned the job-specific estimates derived from the statistical model. If there were fewer than five measurements for a particular job, the mean of all jobs with the same prior exposure rating within the same unit or major group was applied, using the hierarchical structure of ISCO-68 (Peters *et al.*, 2013).

Jobs classified as non-exposed by DOM-JEM were assigned an exposure level of 0 (f ml^{-1}, mg m^{-3}, or µg m^{-3}) as an override. The proportion of measurements in those non-exposed jobs was 28% for asbestos, 27% for chromium-VI, 24% for nickel, 41% for BaP, and 38% for RCS. These measurements were still included in the model to inform time trends and regional differences. Using the prior exposure rating in the statistical model also allowed for calibration of exposure levels (i.e. low and high) by a weighted mean of exposure measurements. This way, an exposure level for all potentially exposed jobs (even jobs with fewer than five measurements) could be estimated, as has been described previously (Wild *et al.* 2002; Friesen *et al.* 2012).

RESULTS

Table 2 presents the parameter estimates as derived from the full statistical model for each agent, i.e. adjusted for the other variables in the model (job, measurement year, and sampling duration and methods), as well as the variance components.

Table 2. Model output for the five selected agents

	Asbestos		Chromium-VI		Nickel		BaP		RCS	
Fixed effects										
Time trend (% per year, 95% CI)	Before ban: −10.7% (−11.3% to −10.0%) After ban: +1.7% (−0.4% to +3.7%)		−2.7% (−3.2 to −2.3%)		−1.2% (−1.7 to −0.7%)		−1.2% (−3.1 to −0.7%)		−5.5% (−6.0 to −5.0%)	
Trend in exposure level per hour increase in sampling duration (95% CI)	−23.1% (−26.0 to −20.0%)		−15.2% (−16.7 to −13.7%)		−16.9% (−18.6 to −15.3%)		−9.2% (−14.5 to −3.5%)		−9.2% (−10.8 to −7.5%)	
Prior exposure rating (GMR, 95% CI)										
Low versus High	0.83 (0.49 to 1.39)		0.83 (0.57 to 1.22)		1.44 (0.93 to 2.23)		0.60 (0.24 to 1.50)		0.61 (0.44 to 0.85)	
None versus High	0.97 (0.59 to 1.59)		0.58 (0.41 to 0.83)		0.63 (0.42 to 0.93)		0.82 (0.37 to 1.84)		0.63 (0.46 to 0.86)	
Random effects										
Regions (GMR, 95% CI)										
Canada	0.56 (0.28 to 1.12)		1.53 (1.12 to 2.09)		1.65 (1.11 to 2.47)		N/A		2.27 (1.34 to 3.85)	
CEE countries	3.60 (1.76 to 7.34)		1.60 (1.12 to 2.29)		1.05 (0.62 to 1.79)		N/A		2.39 (1.43 to 3.99)	
France	1.14 (0.57 to 2.28)		1.41 (1.04 to 1.90)		1.89 (1.24 to 2.81)		N/A		0.61 (0.36 to 1.02)	
Germany	2.47 (1.23 to 4.97)		0.72 (0.53 to 0.98)		0.76 (0.51 to 1.13)		N/A		0.54 (0.33 to 0.91)	
Italy/Spain	1.41 (0.70 to 2.83)		0.49 (0.35 to 0.68)		0.35 (0.23 to 0.54)		N/A		0.69 (0.40 to 1.18)	
The Netherlands	2.47 (1.23 to 4.97)		1.05 (0.73 to 1.50)		1.35 (0.86 to 2.13)		N/A		1.53 (0.89 to 2.62)	
Sweden	0.37 (0.18 to 0.76)		0.90 (0.67 to 1.23)		1.20 (0.80 to 1.79)		N/A		0.53 (0.32 to 0.89)	
UK	0.34 (0.17 to 0.67)		0.86 (0.63 to 1.19)		0.71 (0.47 to 1.06)		N/A		2.39 (1.43 to 3.99)	
Variance components (SE)										
Null model										
Between jobs	1.20 (0.12)		0.77 (0.08)		1.22 (0.12)		3.18 (0.41)		0.87 (0.09)	
Between regions	0.29 (0.17)		0.26 (0.14)		0.19 (0.10)		2.32 (1.28)		1.14 (0.66)	
Residual	2.58 (0.02)		4.11 (0.04)		4.19 (0.04)		7.08 (0.15)		3.96 (0.04)	
Final model		Explained		Explained		Explained		Explained		Explained
Between jobs	0.88 (0.09)	27%	0.76 (0.08)	1%	0.94 (0.10)	23%	2.94 (0.39)	8%	0.71 (0.08)	18%
Between regions	0.86 (0.50)	0%	0.17 (0.10)	35%	0.31 (0.17)	0%	2.97 (1.65)	0%	0.47 (0.27)	59%
Residual	2.46 (0.02)	5%	3.79 (0.03)	8%	4.11 (0.04)	2%	6.75 (0.15)	5%	3.87 (0.04)	2%

BaP, Benzo(a)pyrene; CEE, Central and Eastern European countries; CI, confidence interval; GMR, geometric mean ratio; N/A, not applicable; SE, standard error; RCS, respirable crystalline silica.

Time trends in the periods covered by personal measurements varied from −1.2% per year for BaP (95% confidence interval (CI) −3.1% to −0.7%) and nickel (95% CI −1.7% to −0.7%) to −10.7% (95% CI −11.3% to −10.0%) for asbestos exposure before a ban was implemented (Table 2). The geometric mean ratio (GMR) for asbestos concentrations before and after the ban was 3.06 (95% CI 2.65 to 3.54; data not shown). The time trend after implementation of the bans was estimated to be +1.7%, but this was not statistically significant (95% CI −0.4% to +3.7%).

The ratios for low versus high exposed jobs were not statistically significant and ranged from 0.60 for BaP to 0.83 for both asbestos and chromium-VI exposure. For nickel exposure the ratio was in the reverse direction (1.44). Figure 1 shows the distribution of job-level estimated exposure levels for exposed jobs between 1970 and 2010, for asbestos, chromium-VI, nickel, and RCS, stratified by prior exposure ranking. The fold-ranges between the 5th and 95th percentile of job-specific estimates (exposed jobs only) were 8.9 for asbestos, 9.8 for chromium-VI, 10.3 for nickel, and 12.5 for RCS, while interquartile ranges were 2.1, 2.3, 2.2, and 2.5, respectively (data not shown).

Region-specific estimates were in some cases combined due to limited data: the RCS estimate for the UK was also assigned to the CEE countries (Peters *et al.*, 2013) and Germany and the Netherlands were combined into one region for the asbestos estimate. For BaP exposure, no random effects (i.e. no job- or region-specific estimates) were assigned because too few data points were available. CEE countries showed the highest GMs overall. The ratio between the highest and the lowest region estimate varied by agent; ranging from a factor 3.3 for chromium-VI to 10.5 for asbestos exposure.

The GMR for chromium-VI and total chromium was 3.10 (95% CI 2.94 to 3.28; data not shown), indicating that, e.g. a level of 1.5 μg m^{-3}

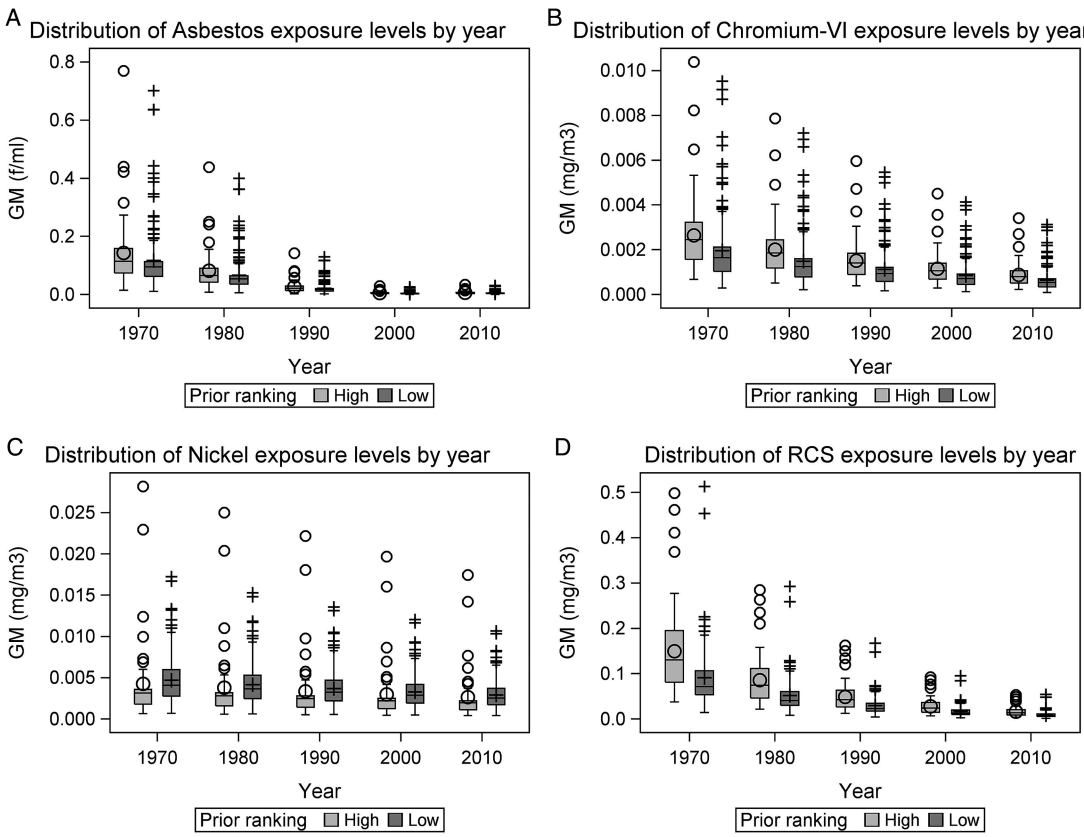

Figure 1 Distribution of the job-level estimated exposure levels for exposed jobs between 1970 and 2010.

chromium-VI corresponded to a level of 4.7 μg m^{-3} total chromium.

Mean estimates for low and high exposed jobs (i.e. the calibrated *a priori* exposure rating), plus the estimates for the 10 highest exposed jobs per agent are presented in Tables 3–6. Exposure levels are given for the years 1980 and 2000 (without a region effect), standardized to an 8-h work-shift. For asbestos, these years represent levels before and after a ban implementation. Job-specific estimates were not assigned for BaP; mean estimates in 1980 were 0.019 and 0.032 μg m^{-3} for low and high exposed jobs, respectively. BaP estimates in 2000 were 0.015 μg m^{-3} for low exposed jobs and 0.025 μg m^{-3} for high exposed jobs.

DISCUSSION

We have elaborated empirical models using personal occupational exposure measurement data for five major lung carcinogens to estimate occupational exposure levels for multiple decades, jobs and countries/regions. Based on these models we have developed the quantitative SYN-JEM. The model structure aimed to take into account job title, year, region, *a priori* exposure rating of each job (for extrapolation to unmeasured jobs and to override biased sampling results), sampling and analytical methods, measurement strategy and sampling duration.

Use of measurements and prior exposure ratings

Occupational exposure measurements for a wide range of countries were collected in the ExpoSYN database (Peters *et al.*, 2012). Statistical modelling resulted in job-, region-, and time-specific estimates for asbestos, chromium-VI, nickel, and RCS. For BaP, the collected data (n = 4477) hindered the use of job- or region-specific estimates, indicating the importance of large

Table 3. Model-based estimates of exposure levels (geometric mean in 1980 and 2000) and the number of measurements available for the specific job title: asbestos

		Exposure level (GM)		Measurements in model
Calibrated a priori exposure rating		**1980**	**2000[a]**	***N***
Mean estimates	Low exposed jobs	0.061 f ml^{-1}	0.004 f ml^{-1}	7206
	High exposed jobs	0.074 f ml^{-1}	0.005 f ml^{-1}	12 922
Ten highest exposed jobs				
ISCO-68	**Job description**	**1980**	**2000[a]**	
0-35.50	Heating, ventilation, and refrigeration engineering technician	0.439 f ml^{-1}	0.029 f ml^{-1}	159
7-52.20	Spinner, thread, and yarn[b]	0.407 f ml^{-1}	N/A	681
7-52.30	Doubler[b]	0.256 f ml^{-1}	N/A	578
7-52.50	Winder[b]	0.248 f ml^{-1}	N/A	48
9-56.20	Building insulator (hand)	0.244 f ml^{-1}	0.016 f ml^{-1}	48
9-54.45	Ship joiner	0.236 f ml^{-1}	0.016 f ml^{-1}	20
7-52.40	Twister[b]	0.229 f ml^{-1}	N/A	5
7-54.25	Loom threader (machine)[b]	0.229 f ml^{-1}	N/A	75
0-14.20	Chemistry technician	0.180 f ml^{-1}	0.012 f ml^{-1}	30
8-74.50	Metal shipwright	0.176 f ml^{-1}	0.012 f ml^{-1}	10

[a]Assuming the ban implementation in 1995: no asbestos manufacturing anymore.
[b]Only when in 'Manufacture of non-metallic mineral products not elsewhere classified', which includes all asbestos product making industries.

Table 4. Model-based estimates of exposure levels (geometric mean in 1980 and 2000) and the number of measurements available for the specific job title: chromium-VI

		Exposure level (GM)		Measurements in model
Calibrated a priori exposure rating		**1980**	**2000**	*N*
Mean estimates	Low exposed jobs	0.0012 mg m^{-3}	0.0007 mg m^{-3}	5674
	High exposed jobs	0.0015 mg m^{-3}	0.0009 mg m^{-3}	11 975
Ten highest exposed jobs				
ISCO-68	**Job description**	**1980**	**2000**	
8-72.35	Resistance welder	0.0079 mg m^{-3}	0.0045 mg m^{-3}	30
8-73.20	Sheet-metal marker	0.0072 mg m^{-3}	0.0041 mg m^{-3}	8
7-29.00	Metal processors nec	0.0069 mg m^{-3}	0.0040 mg m^{-3}	99
8-73.50	Boiler smith	0.0066 mg m^{-3}	0.0038 mg m^{-3}	13
7-26.00	Metal annealers, temperers, and case hardeners	0.0062 mg m^{-3}	0.0036 mg m^{-3}	63
9-51.25	Bricklayer (chimney building)	0.0058 mg m^{-3}	0.0033 mg m^{-3}	5
7-22.00	Metal rolling mill workers	0.0053 mg m^{-3}	0.0031 mg m^{-3}	40
8-72.50	Flame cutter (hand)	0.0050 mg m^{-3}	0.0029 mg m^{-3}	145
8-33.70	Precision-grinding machine setter operator	0.0049 mg m^{-3}	0.0028 mg m^{-3}	57
8-99.00	Glass formers, potters, and related workers nec	0.0044 mg m^{-3}	0.0025 mg m^{-3}	22

nec, not elsewhere classified.

amounts of measurement data for statistical modeling. However, even with lower numbers of measurements, a model including the *a priori* exposure rating of all jobs (here by using DOM-JEM) enabled calibration of 'low' and 'high' exposure. In sensitivity analyses for RCS exposure we have previously shown that the model without region- and job-specific estimates (i.e. the mean exposure estimates, or the calibrated JEM) resulted in cumulative exposure levels that were significantly correlated to the levels estimated by the full model ($R_p = 0.74$ for all subjects and $R_p = 0.58$ for RCS exposed only) (Peters *et al.*, 2013).

In addition to estimating quantitative exposure levels for jobs without sufficient measurement data, the prior exposure rating enabled us to apply an override for jobs *a priori* classified as non-exposed. This override prevents assigning exposures to a job title when measurements were taken only in extraordinary situations. For example, when asbestos exposure was measured for teachers during construction work in school buildings, the override would prevent all school teachers to be assigned asbestos exposure as that would not be their typical occupational exposure and result in extensive misclassification. Between 24 and 41% of the personal measurements for the selected agents in the ExpoSYN database were associated with jobs classified as being non-exposed. Those measurements were still included in the model, providing information to estimate model parameters such as trends, measurement strategy, sampling and analytical methods and regional differences, but their job-specific estimates were not assigned in SYN-JEM. Analyses with models excluding the measurements for non-exposed jobs revealed that fixed-effect estimates only

Table 5. Model-based estimates of exposure levels (geometric mean in 1980 and 2000) and the number of measurements available for the specific job title: nickel

		Exposure level (GM)		Measurements in model
Calibrated a priori exposure rating		**1980**	**2000**	*N*
Mean estimates	Low exposed jobs	0.004 mg m^{-3}	0.003 mg m^{-3}	6178
	High exposed jobs	0.003 mg m^{-3}	0.002 mg m^{-3}	10 503
Ten highest exposed jobs				
ISCO-68	**Job description**	**1980**	**2000**	
8-39.30	Locksmith	0.081 mg m^{-3}	0.063 mg m^{-3}	29
7-28.50	Metal sprayer	0.025 mg m^{-3}	0.020 mg m^{-3}	232
8-72.50	Flame cutter (hand)	0.020 mg m^{-3}	0.016 mg m^{-3}	61
8-71.30	Marine pipe fitter	0.017 mg m^{-3}	0.013 mg m^{-3}	19
7-29.90	Other metal processors	0.015 mg m^{-3}	0.012 mg m^{-3}	59
7-22.00	Metal rolling-mill workers	0.015 mg m^{-3}	0.012 mg m^{-3}	21
8-73.30	Coppersmith	0.012 mg m^{-3}	0.012 mg m^{-3}	10
7-29.00	Metal processors nec	0.012 mg m^{-3}	0.009 mg m^{-3}	82
7-21.70	Furnace man (non-ferrous metal converting and refining)	0.011 mg m^{-3}	0.009 mg m^{-3}	6
8-73.20	Sheet-metal marker	0.010 mg m^{-3}	0.009 mg m^{-3}	6

nec, not elsewhere classified.

slightly changed. The correlation between job-specific estimates resulting from these analyses and the original models were high ($R_p > 0.97$) for all agents, indicating that our models were robust.

The ratio of 1.44 for low versus high nickel exposure implies that jobs *a priori* rated as low exposed showed higher mean levels of exposure to nickel than jobs assigned as high exposed. Although the 95% CI included the null value of 1, this ratio may point towards misclassification of jobs in DOM-JEM or towards bias in the measurement data. Then again, for both low and high exposed rated jobs, higher mean exposure levels were reported in comparison with the jobs classified as non-exposed. Besides the estimate for the *a priori* exposure rating, job-specific estimates will determine the final exposure estimates for a specific job. When omitting the *a priori* exposure rating in the prediction model for nickel, the ranking of jobs was essentially the same ($R_p = 0.98$).

We further observed ratios of 0.83 (asbestos and chromium-VI), 0.60 (BaP), and 0.61 (RCS) for low versus high exposed jobs, representing factors between 1.2 and 1.7. This contrast is considerably lower than the generally assumed factor of 4–5 between low and high exposed jobs in JEMs (Stewart and Herrick, 1991; Semple *et al.*, 2004). Jobs rated as low exposed might be more likely to be monitored in situations where exposures are more likely to occur or are higher (worst case). Such measurement bias results in a lower contrast between low and high exposed jobs. Lack of additional information on the extent of potential bias in the underlying measurement data hindered adjusting the means of the low and high exposed jobs. However, contrast was considerably increased by assigning the job-specific estimates. The fold-ranges for the 5th to the 95th percentiles indicated that there was a reasonable contrast between the higher and lower end of the exposure ranges in exposed jobs (factors between 8.9 and

Table 6. Model-based estimates of exposure levels (geometric mean in 1980 and 2000) and the number of measurements available for the specific job title: RCS

		Exposure level (GM)		Measurements in model
Calibrated a priori exposure rating		**1980**	**2000**	***N***
Mean estimates	Low exposed jobs	0.041 mg m^{-3}	0.006 mg m^{-3}	9406
	High exposed jobs	0.066 mg m^{-3}	0.011 mg m^{-3}	6133
Ten highest exposed jobs				
ISCO-68	**Job description**	**1980**	**2000**	
9-51.25	Bricklayer (chimney)	0.29 mg m^{-3}	0.10 mg m^{-3}	69
8-20.90	Stone cutters and carvers	0.28 mg m^{-3}	0.09 mg m^{-3}	89
8-20.80	Monument carver (hand)	0.26 mg m^{-3}	0.09 mg m^{-3}	396
7-11.70	Sampler (mine)	0.26 mg m^{-3}	0.08 mg m^{-3}	12
9-59.45	Demolition worker	0.26 mg m^{-3}	0.08 mg m^{-3}	147
7-12.20	Stone splitter	0.23 mg m^{-3}	0.07 mg m^{-3}	80
8-20.70	Stone carver (hand)	0.16 mg m^{-3}	0.05 mg m^{-3}	54
8-99.40	Clay slip maker	0.15 mg m^{-3}	0.05 mg m^{-3}	19
7-11.05	Miner (general)	0.14 mg m^{-3}	0.05 mg m^{-3}	253
8-99.30	Clay mixer	0.13 mg m^{-3}	0.04 mg m^{-3}	19

12.5). However, the bulk of the job-specific estimates showed less contrast, since the interquartile ranges of job-estimates were all between 2.1 and 2.5. The lower contrast is a consequence of the applied model structure in which job titles were treated as random effects, where the job-specific estimate was shrunk towards the overall mean where measurements were scarce or highly variable. More measurements with lower variability within a job title would have resulted in more distinct estimates (Friesen *et al.* 2012). In the Shanghai Women Health Study, smaller influence of job/industry-specific estimates were observed for lead when compared to benzene exposure, potentially due to the number of measurements available for the respective agents (Koh *et al.* 2014).

Variance components differed across agents. The explained variance between jobs ranged from 1% for chromium-VI to 27% for asbestos (Table 2). Between-region variance was explained for 35% in the nickel model and 59% in the RCS model, whereas the fixed effects in the models for asbestos, nickel and BaP did not explain any of the between-region variance. The residual variance was by far the largest for all agents, covering the variability between plants, between workers and from day-to-day. Information to explain this variability was not available. Most industry-based studies would be able to describe such variance better, due to more detailed information about work performed, local factory-specific conditions, control measures, etcetera. However, such information would only lead to improved exposure assessment in a community-based epidemiological study of chronic diseases when this detailed information is also available in the work history for each study subject.

Despite the exclusion of extremely short measurements (<60 min), statistical models for asbestos showed a steep decrease in exposure level per hour increase of sampling duration (−23%). This decrease most likely reflects more specific task-based measurements in the lower range of sampling duration, emphasising the importance of standardization to a representative eight-hour work-shift when modeling

exposure measurements with varying sampling times when estimating long-term average exposures for individual workers.

The model to estimate chromium-VI levels comprised measurements for both chromium-VI (35%) and total chromium (65%). The ratio between chromium-VI and total chromium levels was 3.1. However, the ratio may be dependent on exposure circumstances (e.g. material used or task performed). The amount of data did not allow for modelling 'chromium type' as an industry- region- or time period-specific effect. A model including chromium-VI measurements alone revealed similar overall estimates. The time trend was somewhat steeper: −3.5% compared with −2.7%. The region effects were comparable, only Sweden rose to second highest exposed region, while it was lower in ranking when based on all chromium measurements together. The GMR for low versus high exposed jobs was 1.0 when only chromium-VI measurements were modeled. The correlation between job-specific estimates resulting from the model with only chromium-VI measurements and the model with all chromium measurements was moderate (R_p = 0.49). Given the much lower numbers for chromium-VI measurements (one-third of the total number of chromium measurements) we considered using all chromium measurements, and consequently standardizing to chromium-VI, the best option.

Time trends

Over the last decades, occupational inhalation exposure levels have generally been decreasing in western industrialized countries (Creely *et al.*, 2007). We also observed downward trends for all selected agents albeit to a varying degree. Temporal trends in exposure levels may vary between industries and countries, but due to data limitations we were not able to estimate industry- or region-specific trends. Because we applied an overall time trend per agent, direct comparison with time trends in industry-specific studies is not straight forward. However, since the direction and order of magnitude are similar to what has been described in the peer-reviewed literature, we are confident that our estimated time trends are realistic. Still, these general trends may potentially have led to under- or overestimation of exposure levels in particular industries.

For asbestos, the data showed an annual decrease of −10.7% (95% CI −11.3% to −10.0%) before and no further downward trend after the introduction of bans. This steep decrease is likely the result of the growing awareness of asbestos hazards and the final introduction of bans on asbestos. A similar exposure trend of −11% per year has been described for mechanics in the US between 1970 and 1980 (Paustenbach *et al.*, 2003), and −12% per year from 1990 to 2008 in Finland across all industries (Kauppinen *et al.*, 2013). The Finnish trend was even stronger in the earlier decades [−17% per year between 1970 and 1990 (Kauppinen *et al.*, 2013)]. Coble *et al.* (2001) reported an annual decrease of −5% (95% CI −10% to 1%) for asbestos exposure in the US paper and pulp industry from 1979 to 1996.

Although awareness of asbestos hazards was present well before introduction of the actual bans, we treated the year of complete ban as the changing point. Parameter estimates remained largely unaffected when shifting this point to an earlier time (for example in 1980 in the Nordic countries; 1990 in western and southern Europe; and 1995 in CEE and Canada). The only change was for the time trend (which resulted in −10.5% before and −2.8% after the ban), and a smaller ratio between concentrations before and after the ban: 1.70 (95% CI 1.46 to 1.99). These findings show that our assumption that the time trend accounts for the rising awareness before the actual asbestos ban implementation was most likely.

The chromium-VI model showed a downward trend of −2.7% (95% CI −3.2 to −0.7) per year. Previously, different time trends have been described for chromium. In the Netherlands, a decrease of −4% per year was reported for exposure to welding fumes (Creely *et al.*, 2007), one of the major activities for exposure to chromium-VI. In the US paper and pulp industry, however, an increase in chromium exposure of +4% over time was observed for the period from 1979 to 1996, although with a wide 95% CI (−9% to 18%) (Coble *et al.*, 2001). Another US study showed a clear decrease in chromium-VI exposure of about 8–9% annually in a chromate production plant over the years 1940–1972: average concentrations in the production areas decreased from 0.72 mg m^{-3} in the 1940s to 0.039 mg m^{-3} in the period after 1964 (Proctor *et al.*, 2004).

A relatively small temporal decrease in concentrations was observed for nickel exposure (−1.2% per year, 95% CI −1.7 to −0.7). This temporal trend is within the ranges described in previous studies. An exposure trend of −4% per year was reported for welding fumes (Creely *et al.*, 2007), which may contain nickel. Temporal trends in the US nickel industry (1973–1995) ranged from −7.4% (95% CI −8.5 to 6.3) per year for refining to −1.3% (95% CI −4.7 to +2.3) in milling (Symanski *et al.*, 2001).

The BaP model resulted in an overall trend of −1.2% per year (95% CI −3.1 to −0.7). In specific industries, PAH exposure has previously shown to decrease more rapidly over time in road paving (−11% per year) and the aluminium industry (−19%) (Burstyn *et al.*, 2000; Creely *et al.*, 2007).

Regional effects

Regional differences could have resulted from various aspects. As indicated previously, the region/country effect may reflect different working techniques and conditions, or differences in materials used (Peters *et al.*, 2011b). The industrial substructures might be different, depending on type of products or processes. Partly these differences will have been covered by the job code in the model, for example roofers are classified into six groups in ISCO-68, based on the material applied. However, not all codes had the detail to describe subtle regional differences within jobs. For example, miners are described in ISCO-68 as 'workers who extract coal, ores or other solid minerals from an underground or surface mine', whereas mine types and composition of the ore may vary between regions.

Legislation may also have played a role in between-country differences in exposure concentrations (Kauppinen *et al.*, 2000). For asbestos, legislation had a considerable influence, which we aimed to capture by including a country-specific year of asbestos ban implementation as a fixed effect into the statistical model.

The differences between the region estimates varied per agent, but were highest for asbestos with a factor 10 between Sweden and the UK on the one hand and CEE countries on the other. Noteworthy is the high estimate for Germany (and the Netherlands as they were combined with Germany in the asbestos model). Asbestos measurements from Germany were predominantly taken after the implementation of an asbestos ban, while 80% of the overall asbestos measurements represented the pre-ban period (Supplementary Table S2). This imbalance in data may have attributed to the higher overall region-estimate for Germany.

Regional differences in exposure levels may also be influenced by country-specific measurement devices or analytical methods. For asbestos, however, EM was only used in Germany and we could therefore not discriminate between a potential difference between analytical methods (EM and PCM) and other regional aspects. Whether EM results in higher or lower fibre concentrations than PCM highly depends on the fibre types (Williams *et al.*, 2007). Highly variable conversion factors for PCM to EM have been described in the literature, ranging from 1 to 60 (Hauptverband der gewerblichen Berufsgenossenschaften. Faserjahre report (BK-report 1/2007) 2007; National Research Council, 1984). The vast majority of measurements (>95%) in our database were analysed using PCM, which is the standard method for regulatory compliance and most exposure studies described in literature have used PCM (Williams *et al.*, 2007; Loomis *et al.*, 2010). We applied a conversion factor of 1, as described by the German institute that provided the EM-analysed asbestos measurements (Hauptverband der gewerblichen Berufsgenossenschaften 2007). The use of an alternative factor, assuming that EM overestimates the levels compared to PCM, would have resulted in a lower region estimate for Germany. For illustrative purposes, we tested the model with a conversion factor of 2 instead of 1, resulting in a GMR of 1.37 for Germany (where it was 2.47 in the presented analysis). The estimates for the other regions followed the same ranking, and all other parameter estimates (time trend, jobs, *a priori* exposure rating and sampling duration) remained unchanged. The intercept of the model slightly decreased, which would have led to lower exposure estimates (<10%) overall.

For chromium-VI, nickel and BaP, we applied a fixed conversion factor for sampler type. As use of inhalable sampler type is country-region specific, adjustments for sampler type in the models would have been confounded with actual differences between countries. We therefore relied on extensive experimental wind tunnel data and workplace comparisons of different inhalable dust samples from the CALTOOL project (Mark *et al.*, 2015). The use of different sampling and analytical methods could also have played a role in

the estimation of region-specific differences in RCS exposures, *i.e.* due to variability in sampling efficiency among respirable aerosol samplers, but these differences are considered to be smaller than for inhalable samplers (Görner *et al.*, 2001). Nevertheless, we were not able to adjust for other measurement strategy related factors, which could have resulted in considerable uncertainty in the estimates for region and as such these factors should be interpreted with caution.

Comparison with the literature

Many exposure studies published on asbestos comprise task-based measurements (Williams *et al.*, 2007; Hyland *et al.*, 2010), showing much higher exposure levels than estimated for full-shifts with SYN-JEM. Moreover, arithmetic means (AM) are often presented, which are by definition higher than the GM due to the logarithmic nature of exposure data. Analyses of repeated exposure measurements within groups of workers with the same job at the same location have shown that the median value for the total geometric standard deviation was 2.41 (Kromhout *et al.*, 1993). This finding indicates that for an average group of workers working in the same job at the same location the AM will be a factor 1.47 higher than the GM.

SYN-JEM estimates were comparable with full-shift exposure levels reported in studies other than those included in our study. For example, AMs for eight-hour time-weighted averages (TWA) in the US construction industry (1981–1984) were: 0.20 f ml^{-1} for installation and 0.41 f ml^{-1} for removal of asbestos sheets (Williams *et al.*, 2007). With SYN-JEM we estimated GMs of 0.26 f ml^{-1} for building insulators and 0.07 f ml^{-1} for construction carpenters in 1980. There is no specific ISCO-68 code for asbestos removal workers. Eight-hour TWAs reported for electricians in the early 1990s ranged from 0.001 to 0.05 f ml^{-1} (AM) (Mlynarek *et al.*, 1996; Williams *et al.*, 2007). We obtained a GM of 0.005 f ml^{-1} for electricians in 1990. Levels between 0.01 and 0.42 f ml^{-1} (AM) were reported for roofers in the US (1980–1987) (Williams *et al.*, 2007), where SYN-JEM estimated GMs of 0.01 and 0.03 f ml^{-1} for roofers in 1980 and 1990, respectively.

Our chromium-VI estimates showed similar levels in comparison with published studies. A US study, using data from four data sets mainly from the construction industry, reported median exposure levels to chromium-VI during welding tasks between 0.06 and 1.18 μg m^{-3} (2006–2008) (Meeker *et al.*, 2010). For a general welder in SYN-JEM, exposure to chromium-VI in 2008 was estimated at 0.3 μg m^{-3} (GM) (data not shown). For a boilermaker, the reported GM in 2007–2008 was 1.6 μg m^{-3} (Meeker *et al.*, 2010), where in SYN-JEM an exposure level of 3.8 μg m^{-3} was estimated for the year 2000 (Table 4) and 3.0 μg m^{-3} for the year 2008.

Among welders in the US, mean nickel exposure levels of 0.06 and 0.05 mg m^{-3} were reported for 1995 and 1996, respectively (Susi *et al.*, 2000). SYN-JEM assigns a general welder a much lower exposure level of 0.002 mg m^{-3} in 1996. The US study suffered however from a severe bias since nickel analyses were not performed randomly, but only when welding was performed on nickel containing materials. Another US-based study among boilermakers showed much lower median exposures of 0.001 and 0.002 mg m^{-3} in the $PM_{2.5}$ μm fraction in measurements of 1999 and 2000 (Kim *et al.*, 2003). SYN-JEM assigns boilermakers in those years an exposure of 0.007 mg m^{-3} nickel.

CONCLUSION

Statistical modelling of occupational exposure measurements enabled us to estimate time-, job-, and region-specific exposure levels for four (asbestos, chromium-VI, nickel, and RCS) out of five considered lung carcinogens. The limited number of measurements for PAH (i.e. BaP) did not allow for job- and region-specific estimates. Compared with reported exposure levels from datasets other than included in our study, estimated temporal trends and exposure levels were within the same order of magnitude. Estimations resulting from SYN-JEM therefore appear realistic and point towards a valid method to assess occupational exposures quantitatively in studies of the general population although with uncertainty around these estimates. SYN-JEM will enable quantitative estimations of lifetime exposure to occupational carcinogens for individual subjects within the SYNERGY study and further investigation of the associations with lung cancer risk and estimation of synergistic effects from simultaneous occupational exposures and smoking.

We regard the use of quantitative exposure measurement data in the construction of JEMs as an important

methodological step forward to derive quantitative exposure–response relations between occupational exposures and health effects in community-based studies. Evidence resulting from such community-based studies will strengthen occupational risk assessment that is now predominantly based on industry-based studies that often come with inherent limitations as limited case numbers, the healthy-worker effect and lack of lifestyle data. From our study it is clear that large amounts of exposure measurements for a certain agent (>20 000) are necessary to arrive realistic estimates for all exposed jobs in the community at large. For many exposures, this approach might not be feasible and intensive collaboration among institutions collecting measurements with further standardization is essential.

SUPPLEMENTARY DATA

Supplementary data can be found at http://annhyg.oxfordjournals.org/.

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