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Assessing occupational styrene exposure in the European and US Glass Reinforced Plastics Industry for the period between 1947 and 2020

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ABSTRACT

Background: We aimed to develop a method for assessing occupational styrene exposures for application in epidemiological studies on risks of lymphohematopoietic neoplasms and other malignant and non-malignant diseases in the European and the US glass reinforced plastics industries.

Method: We estimated a linear mixed effects model based on individual airborne personal measurements of styrene from the glass reinforced plastics industry in Denmark, Norway, Sweden, UK, and the US. The most suitable model was chosen based on its predictive power as assessed using cross validation with different combinations of predictors; and by comparing their prediction errors.

Results: We created a database containing 21,201 personal and area measurements but a subset of 14,440 personal measurements that spanned a period from 1962 to 2018, were used in the analysis. The selected model included fixed effects for year, sampling duration, measurement reason, product, process and random effects for country and worker. There was strong agreement between the model's predictions and actual exposure values indicating a good fit (Lin's CCC: 0.85 95% CI 0.84, 0.85). There were regional differences in exposure levels, with the UK and the US having comparable exposures that were higher than those in the Nordic countries. Higher exposures were consistent with measurements collected for inspection purposes, the lamination process, and specific products. Styrene exposure levels have decreased annually on average by 7%.

Conclusion: Our exposure model and the resulting exposure predictions will enable estimation of lifetime occupational exposure for individual workers in the European and the US glass reinforced plastics industry and possibly related health risks among employees. The approach facilitates understanding of the uncertainty in our prediction model and can inform analysis of the bias that application of our exposure assessment approach can produce in epidemiologic analyses of exposure-response associations. Addressing systematic sources of bias can increase confidence in the conclusions of the epidemiologic analysis.

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1. Introduction

Styrene is used as a monomer in the production of polystyrene and styrene copolymers, styrene-butadiene rubbers, and in the manufacture of consumer products including house wares, insulation products, tyres and a wide variety of plastic and synthetic rubber products (IARC, 2018). It was first isolated in 1831 but only became commercially important in the late 1930's when it began to be used in the manufacturing of synthetic rubber (IARC, 1994). Its global market is estimated to be worth around USD 97.3 billion by 2032 (Precedence Research, 2024). Occupational styrene exposure has been linked to neurobehavioral effects (Benignus et al., 2005; Sliwinska-Kowalska et al., 2020), ototoxicity (ATSDR, 2010), neurological diseases (Iversen et al., 2021), autoimmune rheumatological diseases (Hjuler Boudigaard et al., 2020) and hematopoietic, sinonasal and lung cancer (Christensen et al., 2017; Nissen et al., 2018; Bertke et al., 2021; Kogevinas et al., 1994). In 2018, The International Agency for Research on Cancer's Monographs programme classified styrene as probably carcinogenic (Group 2 A), based on limited evidence of an increased risk of lymphohematopoietic malignancies in humans and sufficient evidence of carcinogenicity in experimental animals. This was supported by strong evidence of a mechanism that also operates in humans (IARC, 2018). The highest exposures to styrene occur in the reinforced plastics industry where there is little or no co-exposure to known carcinogens (Van Rooij et al., 2008; Jensen et al., 1990), thus reducing the chance of confounding. Different manufacturing sectors fall under the glass reinforced plastics (GRP) industry with boat building, car manufacturing, and construction among the most prominent.

The main processes during manufacture of GRP products include hand lay-up, spray lay-up, continuous lamination, pultrusion, filament winding and various closed-moulding operations. The individual process steps and the order in which they usually occur are: *"(1) preparation of the mould (polishing and waxing), (2) gel coating, (3) mixing of the resin, (4) preparation of the glass fibre mats, (5) application of glass fibre and resin in the mould (lamination), (6) working of the applied material to remove enclosed air (rolling), (7) curing, (8) trimming, (9) painting of the 'raw' side of the laminate (top coating, optional), and (10) finishing."* (Kogevinas et al., 1994). These are typical across facilities, but practices vary across industrial sub-sectors and between facilities. While in some facilities there is a clear division of labour with workers assigned to one or more of these steps, in others, workers who conduct hand- or spray lay-up, for instance, may also engage in gel-coating, rolling, cutting of fibre mats or other process-related tasks (Crandall, 1982; Kogevinas et al., 1994). Also, techniques such as spray- and hand lamination are often combined in the manufacture of a single product (Crandall, 1982; Kogevinas et al., 1994).

One of the first comprehensive investigations into a possible link between styrene exposure and cancer began in 1982, with the establishment of an European multicentre occupational cohort study comprising 41,167 workers from Denmark, Finland, Italy, Norway, Sweden, and the UK (IARC, 1994; Kogevinas et al., 1994). A job-exposure matrix (JEM) was constructed for the exposure-response analysis (Kogevinas et al., 1994). This JEM was mainly based on styrene measurements in air collected from each country included in the cohort. Exposure metrics considered were length of exposure; cumulative exposure; time since first exposure (TSFE) and average level of exposure. With styrene production continuing apace and its proven presence in human blood (Brugnone et al., 1993), clarifying whether there is a causal association with cancer is important. This requires epidemiological studies that have sufficient power and follow-up time and include accurate exposure estimates in order to evaluate risks for subtypes of leukaemia and lymphoma.

With the aim of investigating the exposure-response relationship between styrene and subtypes of lymphohematopoietic and other malignancies in Europe and the US, cohorts of reinforced plastic workers from Finland, Italy and the UK included in the original European multicentre occupational cohort study (Kogevinas et al., 1994), the Danish cohort (Christensen et al., 2018) and a US cohort (Bertke et al., 2021) have been updated with respect to cancer incidence and mortality (Christensen et al., 2021). To facilitate this investigation, Job Exposure Matrices described so far for the European cohorts only, need to be extended to the US. We aim to develop an empirical exposure model based on personal styrene measurements from all countries in the pooled cohort study and, based on this model, derive quantitative estimates of average, full-shift occupational exposure to styrene for the period between 1947 and 2020. This is the period that is covered by the pooled cohort (Christensen et al., 2021).

2. Materials and methods

2.1. Exposure database

We established a database of personal and area exposure measurements of styrene in air collected within the glass reinforced plastics industry. This contains 21,201 records along with contextual data recorded during measurement surveys. Data from Norway (1974–2018), Sweden (1970–1989), and the UK (1985–2010) were obtained from exposure databases curated by, respectively, the Norwegian National Institute of Occupational Health (STAMI), the Swedish Work Environment Authority (Arbetsmiljöverket), and the Health and Safety Executive that covers England, Scotland, and Wales (Burns and Beaumont, 1989). Data from Denmark (1962–2011) included data from the labour inspectorate (Danish Work Environment Authority, Arbejdstilsynet) supplemented with data obtained from several internal company surveillance programs (Kolstad et al., 2005). The data from the US (1978–1999) were collected during measurement campaigns for two separate research studies (Crandall and Hartle, 1985; Serdar et al., 2006).

Exposure determinants for modelling identified *a priori* included industry, job title, production process, product, resin type, sampling method, sample type (personal or area), sampling duration, measurement date, ventilation, use of personal protective equipment (PPE), the source of the dataset and purpose of measurements (Geuskens et al., 1992; van Rooij et al., 2008; Serdar et al., 2006; Lemasters et al., 1985). The datasets were harmonised to facilitate analyses across countries. This included standardisation of names of production processes (e.g. lamination versus non-production processes), products, and industry.

We excluded all measurements from the database that had:

- insufficient information on production process (task) or measurement purpose,
- no personal breathing zone measurements,
- duration of sampling inconsistent with personal measurement (>720 minutes),
- short sampling durations that would not be representative of full-shift exposures or likely to be associated with worst-case sampling or task-based sampling (<60 minutes).

Further details on the excluded data are provided in the supplementary information (Figure S1). Following exclusions, the final dataset comprised of 14,440 personal measurements (Table 1). Country-specific exposure trends were visualised using locally estimated scatterplot smoothing curves (LOESS) with 75% points to fit (Cleveland, 1979).

For the US data sets, sampling durations were not listed for each individual record. They were therefore set to 480 minutes based on the contextual information in the studies' reports indicating that full-shift personal-breathing-zone measurements were collected (Serdar et al., 2006; Crandall, 1982). Styrene concentrations (mg/m^3) were used as reported in the original datasets with no attempt to adjust to the full-shift (8-hr) time weighted average (Jensen et al., 1990). In order to calculate summary statistics and facilitate modelling of styrene measurement, values less than the limit of detection (LOD) (1.5% of 14,440 records) were imputed per dataset: a maximum likelihood estimate approach was used to fit a lognormal distribution to values above the LOD and, based on this distribution, extrapolated to values below the limit (Helsel and Cohn, 1988). Where LOD was not indicated, the lowest value of the tail end of the distribution was used in lieu of the LOD (Lubin et al., 2004).

2.2. Statistical model

Predictors of styrene exposure were considered from the *a priori* list if their relationships with styrene exposure had a p-value <0.1 in univariate analyses. However, in the final selection the importance of their relationships with styrene exposure based on expert knowledge was also considered. To come to the most parsimonious model, we used 5-fold cross validation to compare the predictive power of models with different combinations of predictors. In k-fold cross-validation, we split the dataset into k samples of equal sizes. Next, we assessed the model's mean-squared error (MSE) on each of this kth sample, while training the model on the k-1 remaining samples. We assessed the improvement of prediction errors by comparing their Akaike Information Criterion (AIC) scores. Marginal and conditional R^2 values for mixed effects models based on Nakagawa and Schielzeth (2013) were also calculated. The conditional R^2 considers both fixed and random effects while the marginal R^2 considers fixed effects only. We made a compromise among these model quality indicators to identify the most suitable model. An additional consideration was what data on predictors used in the model were also available in the study cohort. This was necessary to ensure that the final model selected would be suitable for use in the cohort study for which it was primarily developed.

Due to the lognormal distribution of styrene measurements, the response variable was log-transformed (base *e*). The linear mixed-effect models were fitted via restricted maximum likelihood algorithm using the lmer4 package in R (v1.1-16) (Bates et al., 2015; R Core Team, 2023). The models were of the form $log_e Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \ldots + \beta_q x_q + \mu + \delta + \varepsilon$, where $log_e Y$ is the outcome value (with Y = air styrene concentration (mg/m^3)), β_0, is the intercept, $\beta_{1\ldots q}$ are the coefficients for the fixed effects, $x_{1\ldots q}$ are the values of the predictor variables, μ is the random country effect $\mu \sim N(0, \sigma_c^2)$, δ is the random worker effect $\delta \sim N(0, \sigma_B^2)$, and ε is the random effect of measurements within a worker $\varepsilon \sim N(0, \sigma_w^2)$; all random effects are mutually independent; we assumed the compound symmetry covariance structure of random effects.

Agreement between observed and fitted values and reliability of the model predictions were assessed using Lin's Concordance Correlation Coefficient (Lin's CCC). The sensitivity of the model to measurements collected prior to 1975 when measurement durations were shorter (median duration in minutes was 60 prior to 1975 vs 229 after 1975) was tested by excluding measurements collected prior to 1975. Finally, we also compared the predicted values of the best fitting model with the model that was eventually selected for constructing the exposure matrix. This selection was based on a combination of quality indicators and pragmatic considerations such as availability of data in the cohort dataset.

3. Results

3.1. Database

Our data spanned a 57-year period, from 1962 to 2018 with Denmark and Norway contributing the most complete temporal coverage spanning 40 and 49 years, respectively. Denmark and Norway contributed respectively, 26% and 32%, of the 14,440 records while each of the other three countries contributed approximately 14%. Denmark was the only country to provide measurements from the 1960s with the next earliest measurements from the 1970s, coming from Sweden and Norway. Data from the UK and the US covered mainly the 1980s and 1990s (Table 1 and Fig. 1A). Short sampling durations were typical of measurements collected in the earlier years. Most data were collected during one of the lamination steps (84%) (Table 2). There was a non-monotonic decrease in country-specific time-trends (Fig. 1B).

3.2. Model selection

Initially, industry, process, product, country, sampling duration, reason for measurement and year of sampling were selected as predictor (*x*) variables. In the final model 'industry' was not retained, leaving the fixed effects process, product, measurement reason, sampling duration (minutes) and year of measurement as fixed effects. The most fully parameterised model had a better fit (AIC 45169) compared with the selected model (AIC 45664). However, comparisons of predicted values of these two models showed the predictions to be comparable (Fig. 4). Also, based on the 5-fold cross validation, values of Root Mean Square Error (RMSE) and the Mean Absolute Error (MAE) were comparable (RMSE 0.607 vs 0.608; MAE 0.420 vs 0.421) as were levels of marginal and conditional R^2 (Table 3).

The selected model explained 28% of the total variation in exposure (Table 3). Comparison of the full model (fixed and random effects) with the null model (random effects only) using a likelihood ratio test showed an improvement in model prediction errors with the selected predictors ($\chi^2_{16} = 3603$, $p < 0.001$). The full model (random and fixed effects) explained 73% of the variation while the fixed effects explained 30% indicating that the contribution from random effects (country, workers, and unknown sources) was about 43%. Based on repeated measurements on the same worker it was clear that within-worker (day-to-day) variance contributed substantially to the total variance (53%) while between country and residual variance contributed 9% and 37%, respectively (Table 4). Residual plots did not indicate noticeable deviation from model's assumption of homoscedasticity (Fig. 2). Plots of fitted versus observed values showed a strong agreement (Lin's CCC: 0.85 95% CI 0.84, 0.85) between the model's predictions and actual exposure values (Fig. 3).

The estimated parameters of the final model are summarized in Tables 4 and 5. Data on a larger set of potential exposure predictors

Table 1
Description of the styrene measurements (mg/m^3) by country and time-period.

Country/dataset	N	N < LOD	Nr	Styrene concentration (mg/m^3)			Duration (minutes) AM (range)	Years
				AM	GM	GSD		
Denmark	3851	14	–	201	97	4.2	103 (60–540)	1962–2011
Norway	4649	25	571	143	65	5.7	335 (60–720)	1974–2018
Sweden	2032	3	–	120	66	3.3	158 (60–556)	1970–1989
United Kingdom	2053	6	–	184	112	3.1	241 (60–605)	1985–2010
United States 1	464	0	–	270	218	2.0	480 (480 - 480)	1978
United States 2	1391	141	254	86	32	5.6	480 (480 - 480)	1996–1999
All	14440	189	825	160	76	4.6	250 (60–720)	1962–2018

N – number of measurements; LOD - limit of detection; Nr - number of repeated measurements on workers; AM – Arithmetic mean; GM – Geometric mean; GSD – Geometric standard deviation.

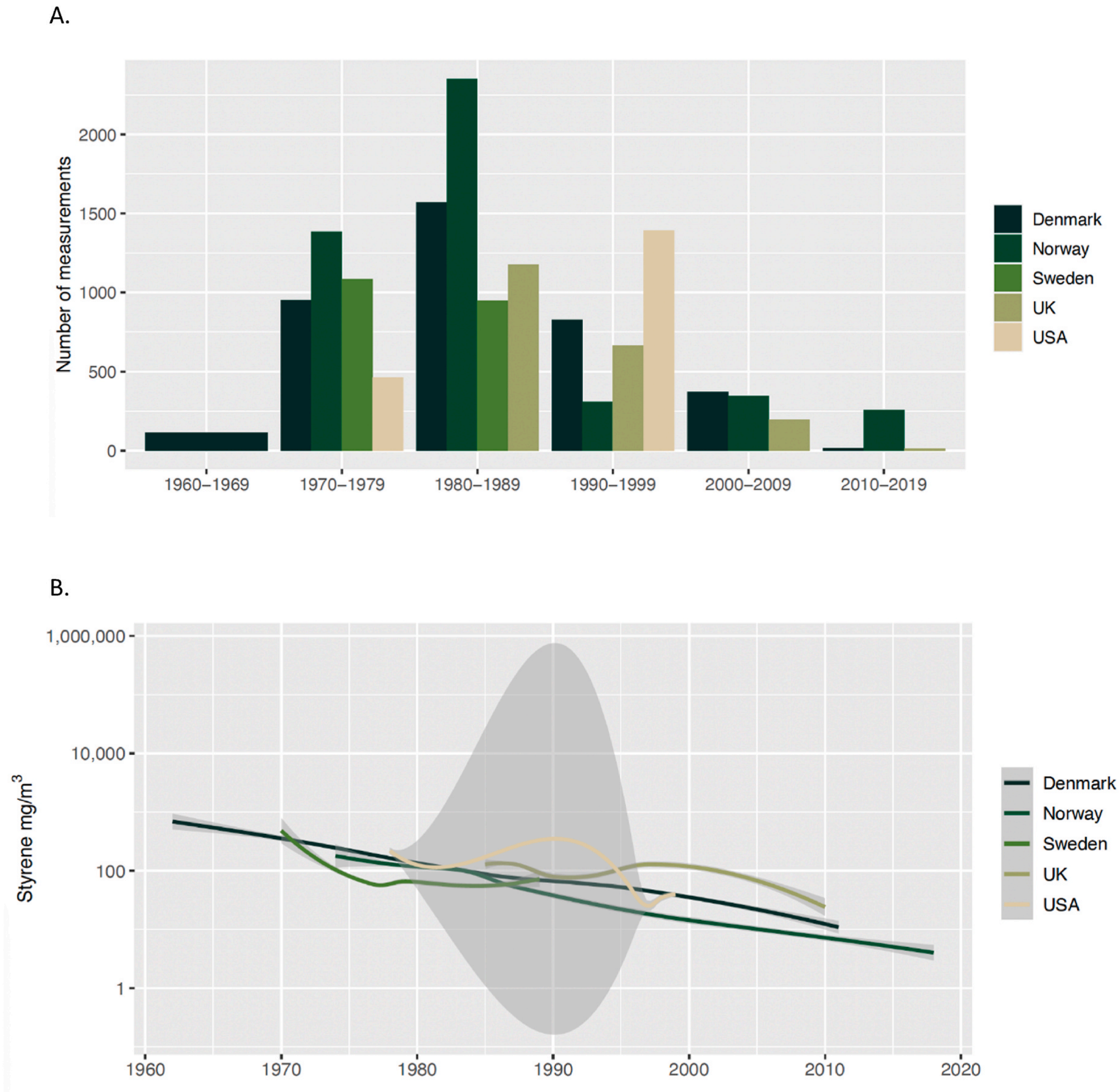


Fig. 1. A. Number of measurements available for modelling by country and decade. B. Observed trends in occupational exposure to styrene (mg/m^3) by country from 1962 to 2018 using Loess-smoothed curves of styrene concentrations with 95% confidence intervals in grey.

including job title, industrial sub-sector, work condition, ventilation and use of PPE were available for a little over 10% of the exposure dataset. These came mostly from the boat manufacturing industry. Due to the limited availability of data on the control measures and the fact that information on job title and industrial sub-sector were not available within most of the sub-cohorts underlying the European multicentre occupational cohort study, we did not retain these predictors in our model. However, for 53% of our data there was a clear relation between product and industrial sub-sector. When the product category was ‘boats’, the industrial sub-sector was ‘manufacture and repair of boats’. This was the case for 35% of the dataset used for modelling. Similarly, when the product was ‘vehicles’ (8%) and ‘construction materials’ (6%) the industrial sub-sectors were ‘manufacture, repair and sale of motor vehicles’ and ‘construction’, respectively. This should have explained some of the variation covered by industrial sub-sector. Model prediction errors somewhat improved when industrial sub-sector was added (AIC from 45664 to 45169), indicating that the specific parameter ‘industrial sub-sector’ potentially accounts for additional industry specific variation not encompassed in product (Table 3). Sensitivity to measurements collected prior to 1975 showed no change in direction of effects and there was minimal change in the effect sizes of the model (Supplementary material: sensitivity analysis).

The estimated model was used to predict the average styrene exposure for a typical worker for each product/process combination by selecting predictor values of ‘routine monitoring’ (not worst-case sampling strategy) for measurement reason and ‘full-shift sampling’ (i.e. 480 minutes) for sampling duration (equation (1)). The arithmetic mean was chosen as is recommended practice for risk assessment for chemical carcinogens (Rappaport, 1991). Estimates of average exposure during normal working conditions were made for every year for which exposure measurements were available. Predictions of mean styrene exposure by country were made by including best linear unbiased predictors (BLUP) of random country (b_c) in the calculations (equation (2)).

$$e^{\beta_0+\beta_{ps}\text{Process}+\beta_{pd}\text{Product}+\beta_{mr}\text{Reason}+\beta_{dr}\text{Duration}+\beta_{yr}\text{Year}+\sigma_w^2/2} \quad (1)$$

$$e^{\beta_0+\beta_{ps}\text{Process}+\beta_{pd}\text{Product}+\beta_{mr}\text{Reason}+\beta_{dr}\text{ Duration}+\beta_{yr}\text{Year}+b_c+\sigma_w^2/2} \quad (2)$$

These estimates were used to construct an exposure matrix where every cell represents the arithmetic mean styrene exposure during the respective process/production combinations for every year from 1947

Table 2
Styrene air exposure measurements used for statistical modelling.

Model parameters		
Categorical predictors	Number	%
Process		
Lamination	12185	84
Other production processes	1272	9
Non-process work	797	6
Area	186	1
Product		
Boats	5036	35
Construction materials	636	4
Containers	594	4
Large parts	3206	22
Mixed products	785	5
Panels	359	2
Pipes and tanks	102	1
Small parts	471	3
Unknown plastic products	2103	15
Vehicles	1148	8
Reason for measurement[a]		
Routine monitoring	5950	41
Worst-case	8171	57
Unknown	319	2
Country		
Denmark	3851	27
Norway	4649	32
Sweden	2032	14
UK	2053	14
USA	1855	13
Continuous predictors	Median (standard deviation)	Range
Year of measurement	1985 (9.5)	1962–2018
Duration of measurements (minutes)	210 (167)	60–720

[a] worst-case – inspection in response to an event; routine monitoring – for benchmarking purposes or research investigating exposure during normal working conditions.

up to 2020 (Supplementary table – available upon request). Predictions of styrene exposure that fell outside the years for which we had measurement data were assumed to be the same as the estimate for the closest year of measurement. Exposures for the years 1947 up to 1961 were assigned the same estimates as for 1962 (Burstyn et al., 2003).

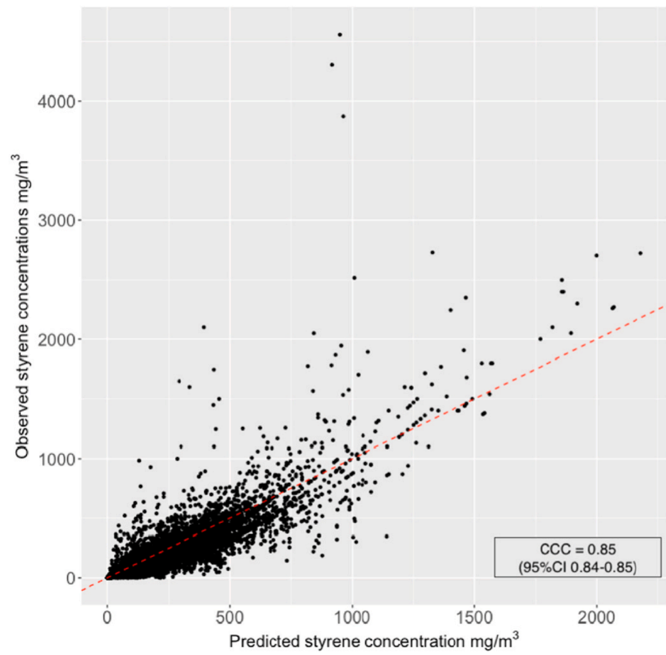


Fig. 3. Plot of observed versus predicted styrene exposure (mg/m^3). The dashed line is the 1:1 line and represents the ideal fit.

Likewise, the years 2019 and 2020 were assigned the levels estimated for 2018.

3.3. Trends in styrene exposure

Based on the final model (Table 5) it was estimated that styrene exposure levels decreased annually on average by 7%, as illustrated in Fig. 1B. Model predictions for earlier years (1962–2000) were less accurate than for more recent years (>2000) with the model tending to overestimate exposure in earlier years (Fig. 4).

The exposure levels captured by worst-case sampling during the lamination of boats, construction materials, panels, and pipes and tanks were associated with the highest exposure levels. Regarding processes,

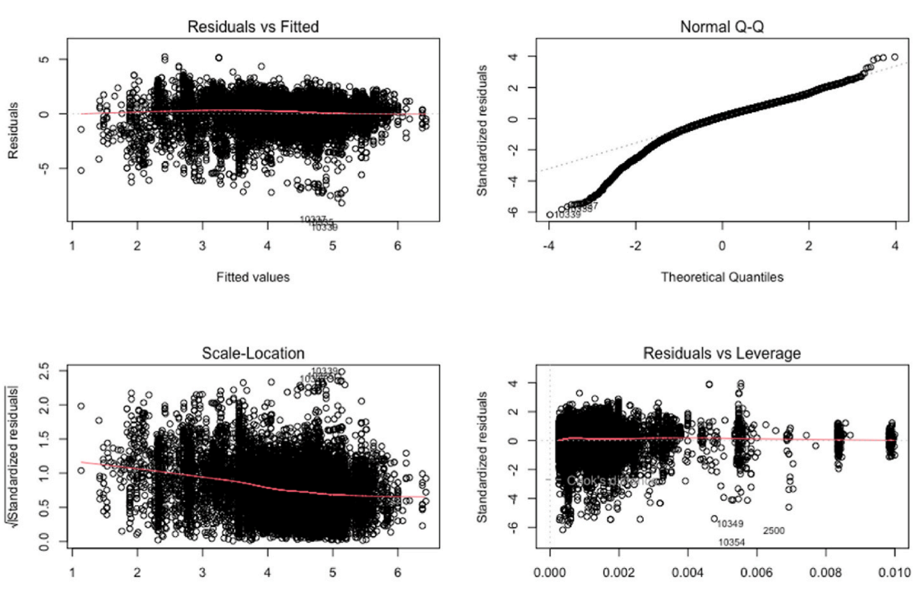
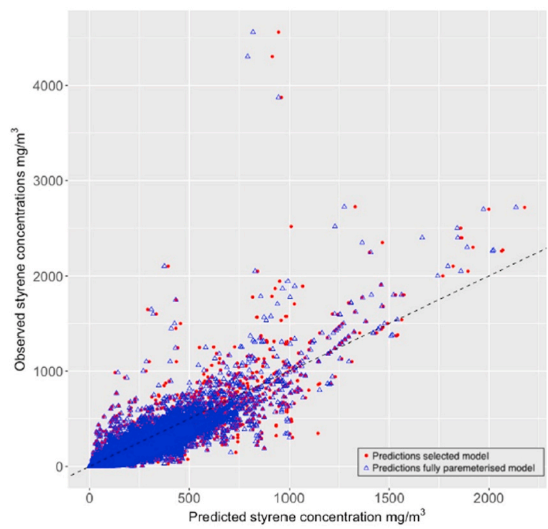


Fig. 2. Diagnostic plots for the styrene exposure model showing: residuals in function of fitted values (top left), normal-quantile-quantile plot (top right), scale-location plot (bottom left), right -leverage plot (bottom right).

A.



B.

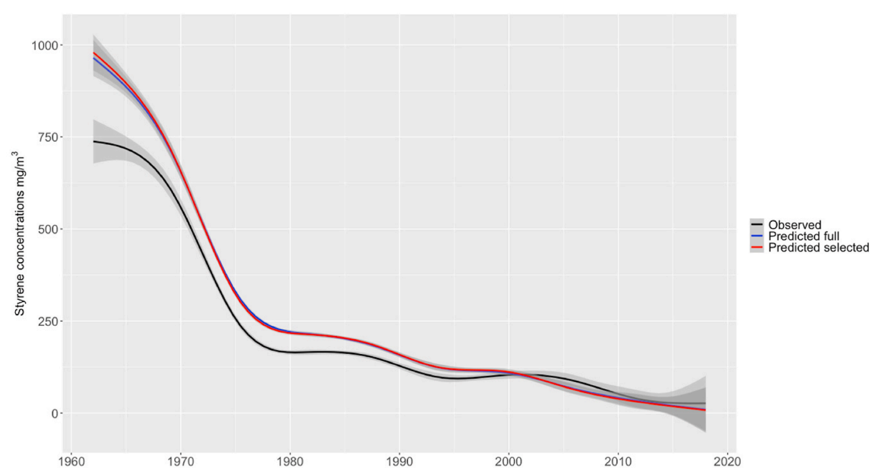


Fig. 4. A. Overlay plot of observed versus predicted styrene exposure (mg/m^3) for the selected model and the fully parameterised model. B. Predicted estimates based on the fully parameterised model and the selected model and observed styrene exposure from 1962 to 2018.

'non-process work' was associated with the lowest exposure relative to lamination (on average, −70%), followed by 'area' that refers to working in the vicinity where lamination tasks are being conducted without engaging in lamination tasks oneself (on average, −59%). 'Other processes' that referred to non-lamination processes were associated, on average, with half of the exposure level relative to lamination.

We estimated that there were differences in exposure levels between countries. Within European countries, the differences were greatest between Sweden and Denmark. There was little difference between the UK and the US with differences between Europe and the US/UK also present. We did not have sufficient information to investigate this further.

4. Discussion

During this study, we created a predictive model based on personal exposure measurements to be used for estimating styrene exposure in an international cohort study on risks of lymphohematopoietic neoplasms, other cancers, and chronic non-malignant diseases in the European and the US glass reinforced plastics industry. The model may also be used in other styrene exposed reinforced plastics cohorts with information about product, process, and calendar year, where there is an indication of similarity in work contexts. Due to limitations imposed by new data sharing legislation (EU, 2016), we were unable to access all the historic styrene exposure datasets that had been used for exposure assessment in the original cohort study by Kogevinas et al. (1994). However, it was possible to include additional exposure data from the US, UK and Norway resulting in this being the most comprehensive international styrene exposure assessment based on the largest number of personal exposure measurements since the 1990s. In the absence of data to perform an external validation the use of cross validation ensured selection of the most robust model.

Like our study, Christensen et al. (2018) reported the highest exposure levels from boat manufacturing companies. Their predictions of styrene exposure intensity were based on a linear mixed effects model at a company level with similar independent determinants to our model (i.e. main production process, main product, and decade). This is not surprising, because their data, covering the period 1970–2011 in the Danish reinforced plastics industry, were a subset of the data used in this study (∼26% of our dataset). Serdar et al. (2006) found that styrene exposure varied by product even when job title was restricted to laminators; we noticed the same pattern. This was true for job titles within

Table 3
Model performance indicators used to inform model selection.

	AIC	5-fold cross validation		R^2	
		RMSE	MAE	con-R^2	mar-R^2
null model 1 – country	52961	1.507	1.113	0.036	0.000
null model 2 – country, participant	49223	1.326	0.368	0.740	0.000
null model 2					
+ year	46580	1.200	0.397	0.754	0.207
+ year, sampling duration	46576	1.199	0.400	0.756	0.214
+ year, sampling duration, product,	46510	1.193	0.397	0.759	0.220
+ year, sampling duration, product, process	45778	1.157	0.419	0.750	0.270
+ year, sampling duration, product, process, measurement reason[a]	**45664**	**0.607**	**0.420**	**0.734**	**0.281**
+ year, sampling duration, industry, process, measurement reason	45280	0.607	0.420	0.728	0.295
+ year, sampling duration, product, process, measurement reason, industry	45169	0.608	0.421	0.731	0.302

[a] Chosen model based on quality indicators and pragmatic considerations (availability of data in cohort); AIC – Akaike Information Criterion; RMSE – root mean square error; MAE – Mean absolute error; con-R^2 – conditional R^2 (considers variance of fixed + random effects); mar-R^2 – marginal R^2 (considers variance of random effects only).

Table 4
Variance components for the null versus the final (full) models.

Variance component	Null model		Full model	
Variance components	Variance (%)	95% CI	Variance (%)	95% CI
Between countries	0.17 (7)	[0.05, 0.66]	0.17 (9)	[0.04, 0.66]
Between workers	1.65 (67)	[1.59, 1.72]	0.96 (53)	[0.91, 1.01]
Within worker	0.64 (26)	[0.61, 0.67]	0.67 (37)	[0.64, 0.69]

CI – confidence interval.

the same industrial sub-sector as well as across industries (not shown). Consequently, depending heavily on job title might introduce error in exposure estimations.

It is difficult to ascribe the reasons for the regional differences that we observed. However, similar country and regional differences have been reported for exposure other than styrene (Basinas et al., 2023; de Vocht et al., 2006; Liu et al., 2011; Peters et al., 2011). Safety culture, workplace practices, workplace layouts and equipment vary across companies, countries, and regions (Deadman et al., 1996; Johansen et al., 2002). The GRP industry is no exception. As previously mentioned, distinct steps in processes could be assigned exclusively to specific workers in some facilities while in others, several steps might be performed by the same worker. For instance, the job title 'gel-coater' or process 'gel-coating' implies that this job title is associated with the distinct tasks of 'gel-coating'. However, this is only true for some facilities. In others, the gel-coater also engaged in other steps in the lamination process. This held to a lesser extent for the job title and process 'moulder' and 'moulding'. Regarding differences in control measures some workplaces partitioned work areas to limit the dispersion of resin to areas not directly engaged in the process (Crandall and Hartle, 1985). Work practices like these required by policies of regional authorities, such as is the case across the European Union, can result in regional

Table 5
Linear mixed effects model parameters for full shift GM personal exposure to styrene in air (ln(mg/m^3)).

	Estimate	95% CI	GMR
Fixed effects			
(Intercept)	137.97	[132.16, 143.77]	
Duration (mins)	−0.0049	[-0.00069, −0.0003]	1.00
Year	−0.067	[-0.07, −0.06]	0.94
Product			
construction materials	0.10	[-0.03, 0.22]	0.90
containers	−0.34	[-0.47, −0.21]	0.71
large parts	−0.08	[-0.16, 0.0038]	0.92
mixed products	−0.49	[-0.6, −0.38]	0.61
panels	−0.26	[-0.41, −0.12]	1.03
pipes and tanks	0.22	[-0.04, 0.48]	1.25
small parts	−0.34	[-0.49, −0.18]	0.71
unknown products	−0.22	[-0.3, −0.13]	0.80
vehicles	−0.12	[-0.23, 0.0019]	0.89
boats	reference		1
Process			
other production processes	−0.72	[-0.80, −0.63]	0.49
non-process work	−1.22	[-1.31, −1.11]	0.30
area	−0.91	[-1.11, −0.71]	0.40
lamination	reference		1
Measurement reason			1.00
reactive	0.25	[0.16, 0.35]	1.28
unknown	−0.24	[-0.44, −0.07]	0.79
non-reactive	reference		1
Random effects			
Country	BLUP		GMR
Denmark	−0.09		1.03
Norway	−0.19		0.82
Sweden	−0.54		0.46
UK	0.41		1.77
USA	0.42		1.77

CI – confidence interval; GMR – geometric mean ratio = exp(Estimate); BLUP – best linear unbiased predictor (b_C in equation (2)).

differences in exposure. Our results suggest that differences in exposure among European countries and regions should be considered when estimating styrene exposure in epidemiological studies, noting that based on our model the differences were more pronounced in the past, certainly before 2000 (details not shown).

We identified repeated measurements from the US and Norway but cannot rule out that there are other repeated measures in our dataset that have not been tagged as such and would have contributed to the residual (within-worker) variance rather than being decomposed into between vs within worker variances. The unidentified repeated measures would also violate the assumption of the residual independence of measurements, but it is difficult to anticipate what bias this may have produced in our predictions. It is likely that a portion of the unexplained variance in our model comes from the between-worker variance that has been attributed to personal factors such as seniority/experience, age, and casual short-term work in the GRP industry (Serdar et al., 2006). Another contributing source would have been the between-facility variation resulting from different work practices and control measures.

The declining time-trend that we observed is consistent with what has been observed across industries using similar modelling approaches (Creely et al., 2007; Basinas et al., 2023; Kromhout and Vermeulen, 2000; Symanski et al., 1998). The accuracy of model predictions improved over the years. This may have been due to the limited availability of data in the earlier time periods along with less consistency in operations, including regulations around control measures, across the industry. However, although in the earlier years (<1975) the model predicts moderately high in terms of absolute exposure values, it reliably identifies relative differences in exposure across all year. Relative differences in exposure between worker/cohort members, which is important for epidemiological analyses, would therefore been correctly assessed. Furthermore, the sensitivity analysis where those measurements were removed showed that this did not appreciably change the model outcome.

The assignment of exposure estimates from 1962 to the years prior to 1962 that were outside the applicable range of the model is a considerable gap, but in the absence of data for that time it is a plausible approach. When faced with a similar challenge of extrapolation back to times where measurements were not available, de Vocht et al. (2009) considered a variety of extrapolations to determine pre-data time--trends. A similar approach can also be implemented in exposure assessment that relies on our models as part of sensitivity analyses (de Vocht et al., 2009). There is less of an issue with the predictions for the recent period of 2019–2020; the 2018 levels were used since there was stability in exposure trends across all countries for the second half of the 2000's indicating that these were the best predictions achievable. Moreover, this becomes irrelevant when applied in the cohort study since with the appropriate lagging of exposure for cancer analyses and, due to the strong decreasing trends over time, the contribution of these 2 years to the overall cumulative exposure is negligible.

Products small enough to be manufactured using machine moulds and closed processes result in lower exposures since workers do not need to be close to the source of styrene (Lenvik et al., 1999). When small items are manually handled in an open process, the exposure potential depends on the number of small parts being made (Crandall, 1982) but is likely to be low relative to the potential exposure when producing large items. Larger items such as (parts of) boats, vehicles, and panels used in construction usually involve manual processes with long periods of exposure close to the source. This, in part, explains the predictive power of product and process over job title. While there is added value in including job title where such information is available it may not appreciably increase the explained variation in multiple regression mixed models for this industry. This lends support for an approach to exposure assessment for the GRP industry that prioritises product and process over job title as predictors of exposure.

Exposure metrics that can be calculated based on the exposure matrix include, but are not limited to, cumulative exposure (mg/m^3-years); average exposure (cumulative exposure/total exposure time (years)); number of (consecutive) years of exposure above thresholds. Our explicit nature of assumptions about exposure assessment captured in our mixed effects models and equations that describe how we assessed exposures created a reproducible method that enables sensitivity analyses exemplified by the work of de Vocht et al. (2009). Our models also provide information about some of the imprecision entailed in such retrospective estimates within the exposure matrix and exposure metrics that result from its application to occupational histories. Understanding uncertainty in our prediction model can inform analysis of the bias that application of our exposure assessment approach can produce in epidemiologic analyses of exposure-response associations, as was done by Sallmén et al. (2024). Addressing systematic sources of bias that arise from complex measurement error structures should aid interpretation of risks attributed to styrene, and increase confidence in the conclusions of the epidemiologic analysis.

5. Conclusions

The styrene exposure predictions based on the statistical model described in this paper were used to construct an exposure matrix that can be used to retrospectively assess the exposure of workers in the reinforced plastics industry for the period 1947 to 2020. This may help to enhance the quality of epidemiological studies on styrene exposure and health effects.

CRediT authorship contribution statement

Yvette Christopher-de Vries: Writing – original draft, Methodology, Formal analysis, Data curation. **Igor Burstyn:** Writing – review & editing, Methodology. **Mette Wulf Christensen:** Writing – review & editing, Data curation. **Hilde Notø:** Writing – review & editing, Data curation. **Kurt Straif:** Writing – review & editing. **Eero Pukkala:** Writing – review & editing. **Vivi Schlünssen:** Writing – review & editing. **Stephen Bertke:** Writing – review & editing. **Martie van Tongeren:** Writing – review & editing. **Henrik A. Kolstad:** Writing – review & editing, Funding acquisition, Conceptualization. **Damien McElvenny:** Writing – review & editing, Supervision. **Ioannis Basinas:** Writing – review & editing, Methodology.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

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Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2024.114494.

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