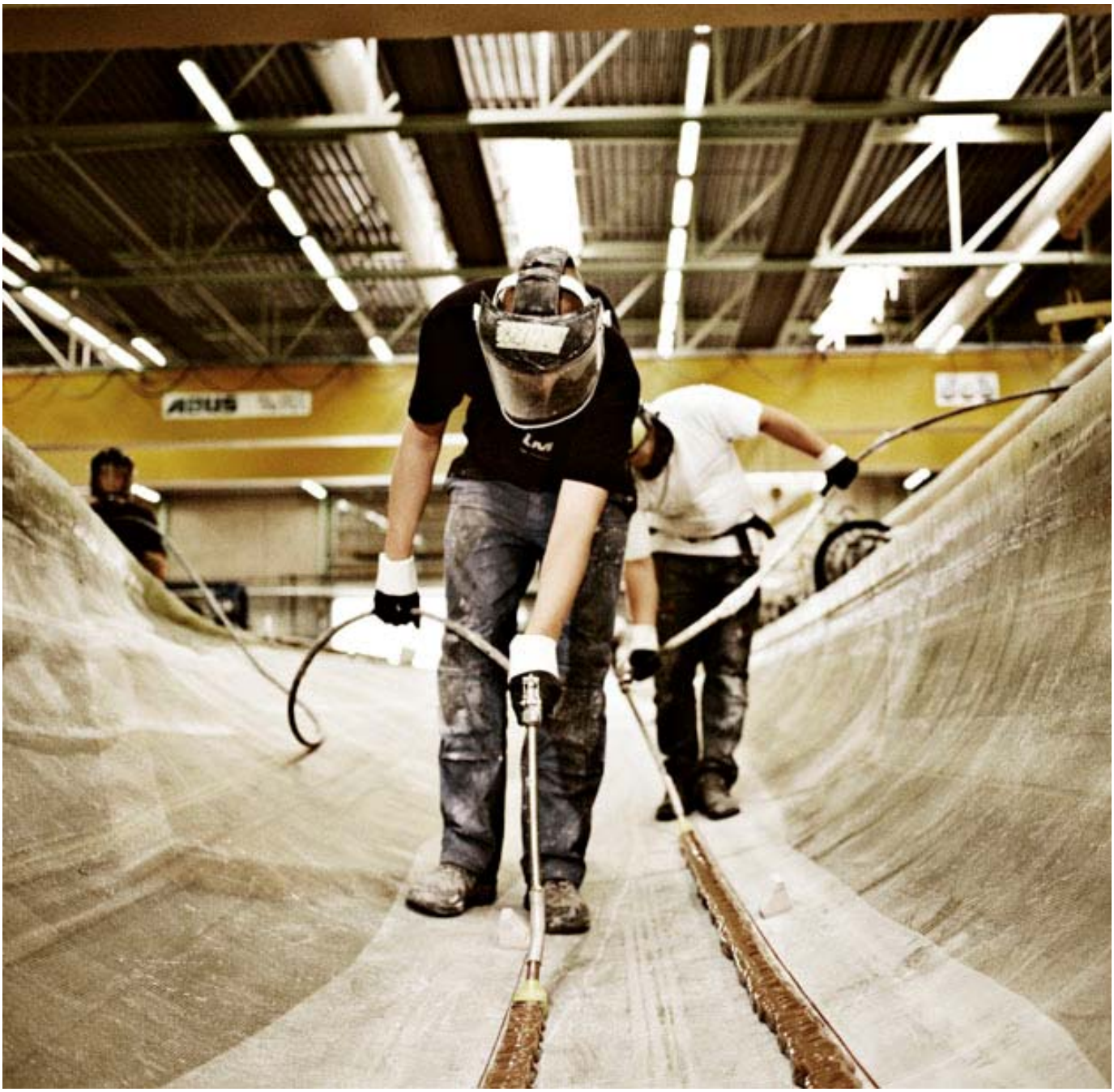
Slutrapport til Arbejdsmiljøforskningsfonden:
Styreneksponering og risiko for kræft: En 40 års opfølgningsundersøgelse af ansatte i den danske glasfiberplastindustri, STRIKT-projektet

Mette Skovgaard Christensen, Mette Schou Nissen, Cæcilia Ramlau-Hansen, Gunnar Vase Toft, Fransesco d'Amore, Inge Brosbøl Iversen, Zara Stokholm, Jesper Medom Vestergaard, Vivi Schlünssen, Jette Sønderskov Gørløv, Johnni Hansen, Henrik Kolstad



Aarhus Universitetshospital-Arbejdsmedicin og Dansk Ramazzini Center, August 2018

Indhold

Forord

Arbejdsmiljøforskningsfonden støttede gennemførelsen af STIKT-projektet (projekt nummer 32-2011-09), som har løbet fra den 1.1.2012 til den 3. august 2018. Denne rapport giver et overblik over de resultater, som er opnået.

Projektgruppen har bestået af Mette Skovgaard Christensen, Aarhus Universitetshospital- Arbejdsmedicin og Center for Registerbaseret Forskning, CIRRAU, Mette Schou Nissen, Inge Brosbøl Iversen, Zara Stokholm, Jesper Medom Vestergaard og Henrik Kolstad, Aarhus Universitetshospital-Arbejdsmedicin, Cæcilia Ramlau-Hansen og Vivi Schlünssen, Institut for Folkesundhed, Aarhus Universitet, Gunnar Toft, Klinisk Epidemiologisk Afdeling, Aarhus Universitet, Fransesco d'Amore, Hæmatologisk Afdeling, Aarhus Universitetshospital, Jette Sønderskov Gørløv, Hæmatologisk Afdeling, Rigshospitalet og Johnni Hansen, Kræftens Bekæmpelse-Center for Kræftforskning.

Mette Skovgaard Christensen har været Phd studerende med Cecilia Ramlau-Hansen, Gunnar Toft, Fransesco d'Amore og Henrik Kolstad som vejledere. Mette Nissen Schou har været forskningsårsstuderende med Zara Stokholm, Vivi Schlünssen og Henrik Kolstad som vejledere. Det Frie Forskningsråd-Sundhed og Sygdom finansierede Mette Schou Nissens scholarstipendium.

Til projektet har der været tilknyttet et advisory board bestående af Elsebeth Lynge, Institut for Folkesundhedsvidenskab, Københavns Universitet, Jens Peter Bonde, Arbejds- og Miljømedicinsk Afdeling, Københavns Universitetshospital, Bispebjerg, Maria Albin, Occupational Medicine-Institute of Environmental Medicine (IMM), Karolinska Instituttet, Sverige, og Manolis Kogevinas, IS Global, Barcelona Institute for Global Health, Spain.

Følgegruppen har bestået af Helle Fabiansen og Christina Busk, Plastindustrien, Michael Jørgensen, CO-industri, Henry Andersen og Sven Rose, 3F, Peter Herskind og Bent Horn Andersen, Dansk Industri, DI.

Vi retter en varm tak til alle deltagende virksomheder og alle ansatte, som har deltaget i projektet, Arbejdsmiljøforskningsfonden og Det Frie Forskningsråd-Sundhed og Sygdom, som gjorde undersøgelsen mulig.

Århus, 3. august 2018,

Henrik Kolstad

Resumé

Styren er et plastkemikalie, som indgår i en række plastprodukter. Almenbefolkningen er udsat for lave niveauer af styren, mens ansatte i plast- og gummiindustrien og specielt glasfiberplastindustrien har været udsat for høje niveauer. Der er udført en lang række epidemiologiske, dyreeksperimentelle og mekanistiske undersøgelser af om styren kan forårsage kræft uden at der er opnået videnskabelig konsensus. Det overordnede formål med STRIKT-projektet var at undersøge om styreneksponering indebærer forøget risiko for kræft.

STRIKT-projektet blev udført blandt 73.000 personer ansat i den danske glasfiberplastindustri siden 1964. Vi identificerede mere end tusinde personbårne målinger af styren udført på mange af virksomhederne. Indtil 1990erne blev måleresultaterne arkiveret af Arbejdstilsynet, og var derfor relativt let tilgængelige, mens dette ikke var tilfældet for senere år. Vi gennemførte også en spørgeskemaundersøgelse blandt 11.000 tilfældigt udtrukne, tidligere ansatte i industrien. Disse data blev anvendt i statistiske modeller til at estimere hver enkelt medarbejders eksponering for styren. Fra Cancerregisteret og Landspatientregisteret fik vi oplysninger om kræftdiagnoser for de knapt 9000 ansatte, som havde udviklet kræft mellem 1968 og 2012.

I statistiske analyser sammenlignede vi forekomsten af 55 kræftformer i undersøgelsespopulationen med forekomsten i den samlede danske befolkning. Vi undersøgte også om risikoen for 22 udvalgte former for leukæmi og lymfekræft samt adenocarcinom i næse og bihuler hang sammen med eksponeringsdosis i interne analyser i studiepopulationen.

Vi fandt stigende risiko for akut myeloid leukæmi med stigende kumuleret styreneksponering, når vi tog højde for en latensperiode på 15 år. Risikoen blandt de højt eksponerede var det dobbelte af de lavt eksponerede. Vi fandt en fem gange forøget risiko for adenocarcinom i næse og bihuler blandt de højt sammenlignet med de lavt eksponerede. Vi fandt ingen holdepunkter for forøget risiko for kræft i lunge, pancreas, øsofagus, nyre eller urinblære; kræftformer som alle har været under mistanke for sammenhæng med styreneksponering, eller øvrige kræftformer.

Resultaterne fra STRIKT-projektet blev i marts 2018 sammen med den øvrige videnskabelig dokumentation vurderet af en ekspertgruppe nedsat af the International Agency for Research on Cancer, IARC. IARC vurderede at STRIKT-projektet bidrog med den mest informative epidemiologiske evidens. De resultater dannede sammen med ny dyreeksperimentel evidens grundlag for at styren blev opklassificeret fra gruppe 2 B, muligt kræftfremkaldende, til gruppe 2A, sandsynligt kræftfremkaldende for mennesker.

STRIKT-projektet har bidraget med væsentlig ny viden, som supplerer dyreeksperimentel evidens og omfattende viden om styrens metabolisme og genotoksiske effekter. Denne viden bidrager til en bredere

forståelse af kemisk karcinogenese, som rækker ud over styren. Projektet har givet ny viden om et kemikalie, som mange er eksponeret for i arbejdsmiljøet og det omgivende miljø, og som må formodes at få afgørende indflydelse på regulering og mærkning af styren internationalt og et sikkert miljø på og udenfor arbejdet. STRIKT-projektet illustrerer de unikke muligheder der er for at udføre høj-kvalitets epidemiologiske undersøgelser i Danmark, når man kan kombinere målinger af kemiske og andre arbejdsmiljøeksponeringer med de omfattende arbejdsmarkeds- og helbredsregistre.

Abstract

Styrene is an important industrial chemical used in the manufacture of a number of plastic products. The general population is exposed to low levels of styrene, while employees in the plastics and rubber industry and especially the reinforced plastics industry have been exposed to high levels. Numerous epidemiological, animal and mechanistic studies have been conducted on the carcinogenicity of styrene without reaching scientific consensus. The overall purpose of the STRIKT project was to investigate whether styrene exposure increases then risk of cancer.

The STRIKT project was conducted among 73,000 employees of the Danish reinforced plastics industry since 1964. We identified more than one thousand personal measurements conducted in many of the employing companies. Until the 1990s, measurement results were filed by the Danish Labor Inspection Authority, and therefore relatively easily accessible, whereas this was not the case for later years. We also conducted a survey among 11,000 randomly selected, former employees of the industry. These data were used in statistical models to estimate each employee's exposure to styrene. From the Cancer Registry and the National Patient Register, we received information about cancer diagnoses for the 9000 employees who developed cancer between 1968 and 2012.

In statistical analyzes, we compared the incidence of 55 cancers in the study population with the incidence in the total Danish population. We also investigated the exposure response relation for 22 selected leukemias, lymphomas and sinonasal adenocarcinoma in internal analyses in the study population. We observed increasing risk of acute myeloid leukemia with increasing cumulative styrene exposure when we considered a latency period of 15 years. The risk among the high-exposed was twice the risk of the low-exposed workers. We observed a five-fold increased risk of sinonasal adenocarcinoma among those with high compared to those with low cumulative exposure. There was no evidence of increased risk of cancers of the lung, pancreas, esophagus, kidney or bladder bladder; cancers that have all been associated with styrene exposure in previous studies, or other cancers.

The results of the STRIKT project were assessed together with other scientific evidence by a group of experts set up by the International Agency for Research on Cancer, IARC, in March 2018. IARC assessed that the Danish study provided the most informative epidemiological findings. IARC concluded that the evidence was sufficient to upgrade styrene from group 2B, possibly carcinogenic, to group 2A, likely carcinogenic to humans.

The STRIKT project has provided new epidemiological insight supplementing evidence from animal experiments and extensive knowledge about the metabolism and genotoxic effects of styrene that contributes to our general understanding of chemical carcinogenesis. The project has provided new knowledge about a chemical that many are exposed to at work and in the environment. This knowledge is supposed to have a

decisive influence on the regulation and labeling of styrene internationally and a safe environment on and off the job. The STRIKT project illustrates the unique possibilities for performing high-quality epidemiological studies in Denmark, when combining measurements of chemicals and other occupational exposures with the comprehensive labor market and health registers available.

Baggrund og formål

Styren er et plastkemikalie, som indgår i syntetisk gummi, isoleringsmaterialer, engangsservice, emballage, glasfiberplast og en række andre plastprodukter. Der produceres årligt omkring 20 millioner tons styren internationalt. Almenbefolkningen er udsat for lave niveauer af styren, mens ansatte i plast- og gummiindustrien og specielt glasfiberplastindustrien har været udsat for høje styrenniveauer i arbejdsluften. Siden man i 1970erne observerede en ophobning af leukæmi på en fabrik, som anvendte styren i produktionen, har man haft mistanke om at styren er kræftfremkaldende, og der er efterfølgende udført en lang række epidemiologiske, dyreeksperimentelle og mekanistiske undersøgelser af styren. Det overordnede formål med STRIKT-projektet var at undersøge om styreneksponering indebærer forøget risiko for kræft.

Metoder og udførelse

STRIKT-projektet blev udført blandt ansatte i 456 virksomheder, som havde været udsat for styren ved produktion af et både, vindmøllevinger og andre produkter i glasfiberarmeret polyesterplast. Alle 73.000 ansatte i virksomhederne siden 1964 blev identificeret i ATP-registeret. Danmarks Statistik leverede oplysninger om deres erhverv. Vi identificerede mere end tusinde personbårne målinger af koncentrationen af styren i arbejdsluften udført på 133 virksomheder siden 1960erne. Indtil 1990erne blev måleresultaterne udført og arkiveret af Arbejdstilsynet og var derfor relativt let tilgængelige. Fra enkelte virksomheder, som stadigt var i drift, var det muligt at få adgang til målinger udført efter miden af 1990erne. Vi gennemførte også en spørgeskemaundersøgelse af arbejdsopgaver, eksponeringsforhold og livstilsfaktorer blandt 11.000 tilfældigt udtrukne, tidligere ansatte i industrien. Fra Cancerregisteret og Landspatientregisteret fik vi oplysninger om kræftdiagnoser for de knapt 9000 ansatte, som havde udviklet kræft mellem 1968 og 2012. STRIKT-populationen udgør 60 procent af den samlede internationale epidemiologiske studiebase af styreneksponering i glasfiberplastindustrien.

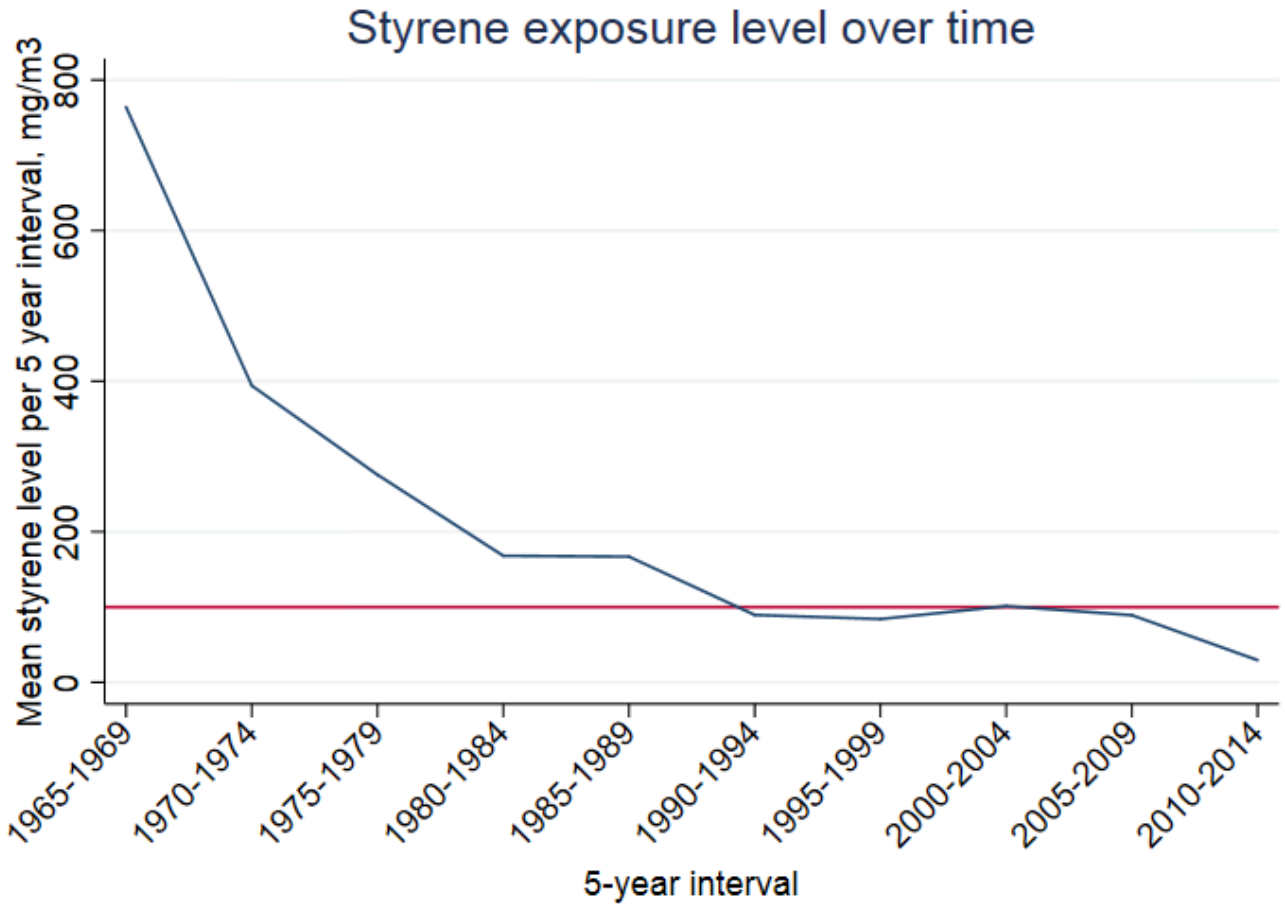
I mixed linear og logistc regressionsmodeller estimerede vi styren eksponeringsintensitet og eksponeringssandssynlighed ud fra oplysninger om produkter, processer, erhverv, kalenderår, virksomhed og virksomhedsstørrelse for hver enkelt medarbejder og beregnede et samlet eksponeringsscore for hele erhvervskarrieren

Vi sammenlignede forekomsten af 55 kræftformer i undersøgelsespopulationen med forekomsten i den samlede danske befolkning ved at beregne standardiserede insidensrater. I interne analyser i studiepopulationen undersøgte vi om risikoen for 22 udvalgte former for leukæmi og lymfekræft hang sammen med forskellige mål for styreneksponering med diskrete time hazard modeller. Vi analyserede også betydningen af tre eksponeringsvinduer: de forudgående <15, 15-29 og ≥30 år.

Takket være studiets størrelse og adgang til detaljerede histologiske oplysninger fra Cancerregisteret, kunne vi også undersøge risikoen for en sjælden form for kræft, adenocarcinom i næse og bihuler, som har veldokumenteret sammenhæng med erhvervsmæssig udsættelse for bl.a. træstøv, og som ser ud til at være særligt sårbar overfor miljøeksponeringer. Til analyser af adenocarcinom i næse og bihuler anvendte vi et nested case control design med individuel aldersmatchning pga. få cases.

Resultater: Om projektets formål er blevet opnået

Vi fandt markant faldende styrenniveauer fra knapt 800 mg/mg^3 i 1960erne til <100 mg/m^{3}i 2010'erne (figur). Grænseværdien er i dag 105 mg/m^3.



Figur. Styren niveauer i den danske glasfiberplastindustri fra 1965-2014, 2508 kort (<1 time) og 1122 langtidsmålinger (≥1 time). Den røde linje angiver den aktuelle grænseværdi på 105 mg/mg^3.

Vi fandt signifikant stigende risiko for akut myeloid leukæmi med stigende kumuleret styreneksponering, når vi tog højde for en latensperiode på 15 år. Risikoen blandt de højt eksponerede var det dobbelte af de lavt eksponerede. Vi fandt mindre konsistente holdepunkter for forøget risiko for T-celle lymfom og Hodgkin lymfom. Vi fandt en fem gange forøget risiko for adenocarcinom i næse og bihuler blandt de højt sammenlignet

med de lavt eksponerede, men kun baseret på 9 kræfttilfælde, og resultatet var ikke statistisk signifikant. Vi fandt ingen holdepunkter for forøget risiko for kræft i lunge, pancreas, øsofagus, nyre eller urinblære, kræftformer som alle har været under mistanke for sammenhæng med styreneksponering i tidligere undersøgelser, eller øvrige kræftformer.

Vi observerede at rygehyppigheden faldt med stigende ansættelsesvarighed i glasfiberplastindustrien, og dette taler i mod at de fundne sammenhænge kan tilskrives confounding fra rygning. Vi havde dog ikke individuelle oplysning om rygning eller andre potentielle confoundere, og dette var en begrænsning ved studiet, men svarer til hvad man har i de fleste studier af industríkohorter, som dette. I analyserne af adenocarcinom i næse og bihuler matchede vi på ansættelse i brancher med mulig træeksponering. Dette må formodes at have reduceret mulig confounding pga. eksponering for træstøv. Informations- og selektionsbias kan næppe forklare fundene, da der ikke indgik selv-rapporterede oplysninger, og data må formodes at være tæt på komplette. Men vi udførte mange analyser, og det kan være at de positive fund var et resultat af tilfældighed.

Erfaringer og konklusioner

Flere epidemiologiske undersøgelser fra andre europæiske lande og USA har tidligere fundet forøget forekomst af uspecificeret leukæmi og lymfekræft blandt styreneksponerede i glasfiberplastindustrien. Men der er få studier, som har haft tilstrækkelig størrelse og adgang til tilstrækkeligt detaljerede oplysninger om specifikke diagnoser. Det er således kun udført få andre undersøgelser af akut myeloid leukæmi og ingen af adenocarcinom i næse og bihuler. Dette gør det på nuværende tidspunkt vanskeligt at sammenholde fundene fra STRIKT-projektet direkte med fundene fra andre studier. På initiativ fra forskerholdet bag STRIKT-projektet er der nu igangsat et internationalt samarbejde for at efterprøve STRIKT-projektets resultater, som bl.a. stiler mod samling og fælles analyse af styrenkohorter i Danmark, Storbritannien, Italien, Finland og USA.

WHOs Agency for Research on Cancer, IARC, har et toneangivende Monografiprogram, som løbende vurderer evidensen for at kemiske stoffer og andre påvirkninger er kræftfremkaldende for mennesker. Resultaterne fra STRIKT-projektet blev i marts 2018 sammen med den øvrige epidemiologiske, dyreeksperimentelle og mekanistiske dokumentation vurderet af en ekspertgruppe nedsat af Agency for Research on Cancer, IARC, hvor Henrik Kolstad deltog. IARC vurderede de danske undersøgelsesresultater som de mest informative blandt de epidemiologiske undersøgelser. De dannede sammen med ny dyreeksperimentel evidens grundlag for at styren blev opklassificeret fra gruppe 2 B, muligt kræftfremkaldende, til gruppe 2A, sandsynligt kræftfremkaldende for mennesker.

Perspektiver: Hvordan projektets resultater på kort og langt sigt kan bidrage til at forbedre arbejdsmiljøet

STRIKT-projektet har bidraget med væsentlig ny viden på internationalt niveau, som supplerer dyreeksperimentel evidens og omfattende viden om styrens metabolisme og genotoksiske effekter. Denne viden vil bidrage til en bredere forståelse af kemisk karcinogenese, som rækker ud over styren.

STRIKT-projektet har givet ny viden om et kemikalie, som har stor udbredelse, og som mange er eksponeret for i arbejdsmiljøet og det omgivende miljø. Denne viden har dannet grundlag for at IARC har opklassificeret dokumentationen for at styren er kræftfremkaldende for mennesker. IARCs vurderinger har afgørende indflydelse på regulering og mærkning af kemikalier internationalt. IARCs opklassificering må formodes at få indflydelse på Det Europæiske Kemikalieagentur, ECHA, som hidtil ikke har klassificeret styren som kræftfremkaldende, og andre regulerende myndigheder. IARCs opklassificering får dog ikke indflydelse på Arbejdstilsynets klassificering af styren i Danmark, da styren allerede er omfattet af Bekendtgørelse om foranstaltninger til forebyggelse af kræftrisikoen ved arbejde med stoffer og materialer (Arbejdstilsynets "kræftliste") qua IARCs hidtidige klassifikation af styren som et 2B karcinogen.

STRIKT-projektet illustrerer værdien af at kunne koble danske registerdata om arbejdsmarked og helbred med centralt registrerede målinger af arbejdsmiljøet. Denne kombination giver unikke data, som muliggør høj-kvalitets epidemiologiske undersøgelser, som kun kan udføres få andre steder end i Danmark. Dette bør forpligte danske myndigheder til, at der igen udføres målinger af kemiske og andre arbejdsmiljøeksponeringer på virksomhederne, som samles i et registrer. Det bør også forpligte danske forskningsmiljøer og fonde til at udnytte disse ressourcer til at undersøge andre arbejdsmiljø påvirkninger, hvor der er mistanke om negative helbredseffekter.

Publikationer og produkter fra projektet

Skriftlig videnskabelig formidling med fagfælle bedømmelse

1. Christensen MS, Hansen J, Ramlau-Hansen CH, Toft G, Kolstad H. Cancer incidence in workers exposed to styrene in the danish-reinforced plastics industry, 1968-2012. Epidemiology. 2017 Mar;28(2):300-10.
2. Christensen MS, Vestergaard JM, d'Amore F, Gorlov JS, Toft G, Ramlau-Hansen CH, Stokholm ZA, Iversen IB, Nissen MS, Kolstad HA. Styrene exposure and risk of lymphohematopoietic malignancies in 73,036 reinforced plastics workers. Epidemiology. 2018 May;29(3):342-51.
3. Nissen MS, Stokholm ZA, Christensen MS, Schlunssen V, Vestergaard JM, Iversen IB, Kolstad HA. Sinonasal adenocarcinoma following styrene exposure in the reinforced plastics industry. Occup Environ Med. 2018 Jun;75(6):412-4.
4. Loomis D, Guha N, Kogevinas M, Fontana V, Gennaro V, Kolstad HA, McElvenny DM, Sallmen M, Saracci R. Cancer mortality in an international cohort of reinforced plastics workers exposed to styrene: A reanalysis. Occup Environ Med. 2018 Apr 17
5. IARC Monographs Vol 121 Group. Carcinogenicity of quinoline, styrene, and styrene-7,8-oxide. Lancet Oncol. 2018 Apr 18. pii: S1470

Øvrig skriftlig videnskabelig formidling

1. Mette Skovgaard Christensen. Styrene exposure and cancer risk in reinforced plastics workers -A long-term cohort study. Phd dissertation, Aarhus University-Health, August 2016
2. Mette Schou Nissen. Sinonasal cancer following occupational styrene exposure: a new signal of human carcinogenesis? Research year report, September 2017.

Mundtlig videnskabelig formidling

1. Mette Skovgaard Christensen. Exposure to styrene and risk of cancer: A 40 year follow-up study of workers in the Danish reinforced plastics industry, Phd day, Aarhus University, Health 2014
2. M.S. Christensen, J. Hansen, C. H. Ramlau-Hansen, G. Toft, H.A. Kolstad. Exposure to styrene and the risk of cancer: a long-term follow-up study of workers in the Danish reinforced plastics industry. The 24th International Epidemiology in Occupational Health (EPICOH) Conference, June 24-27, 2014, Chicago, IL.
3. Mette Schou Nissen, Zara Ann Stokholm, Mette Skovgaard Christensen, Vivi Schlünssen, Jesper Medom Vestergaard, Inge Brosbøl Iversen, Henrik Kolstad. Sinonasal cancer following occupational styrene exposure: a new signal of human carcinogenesis? The 26th International Epidemiology in Occupational Health (EPICOH) Conference, August 28-31, 2017, Edinburgh, Scotland.
4. Inge Iversen, MS Christensen, JM Vestergaard, S Mikkelsen, H.A. Kolstad. Occupational styrene exposure and the risk of encephalopaty and other non-vascular dementia: a long-term follow up study of workers in the

reinforced pastics industry. The 25th International Epidemiology in Occupational Health (EPICOH) Conference, September 4-7, 2016

Mundtlig populær formidling

2012-2016 har Mette Skovgaard Christensen og Henrik Kolstad holdt årlige oplæg om projektets fremdrift og resultater ved Plastindustriens Compositsektions årsmøder

Henrik Kolstad. Arbejde med kemiske stoffer i industrien. Få styr på kemikalierne, Industriens branchemiljøråd, I-BAR, 25. august og 1. september 2015

Øvrige artikler, nyheder og hjemmesider

Stor undersøgelse af kræftrisiko i plastindustrien. CO-magasinet. September 2013

15.000 styren-arbejdere skal undersøges. Fagbladet. 20.11.2013

Tusinder vil fortælle om gul gift. Fagbladet 3F. 05.02.2014

Berygtet plastikmateriale frikendes for en række kræftformer. www.dr.dk/nyheder Syd- og Sønderjylland. 23.12.2016

Opløsningsmiddel frikendes for at øge kræftrisiko. Jyske Vestkysten. 02.02.2017

Den såkaldte »gule gift« i plastindustrien frikendes for at øge risikoen for flere kræftformer. www.b.dk Berlingske. 03.02.2017

Plastindustriens 'gule gift' er bedre end sit rygte. www.AU.dk Newsroom. 03.02.2017

Styrene exposure linked to myeloid leukemia, HL. Hematology Times. 16.02.2017

Opløsningsmiddel, der bl.a. bruges i vindmølleindustrien, er bedre end sit rygte. AU tweet. 2017

After 40 years in limbo: Styrene is probably carcinogenic. www.au.dk/fileadmin/cdn/html/news/news-print_en.html#news-13222 25.05.2018

En uudtømmelig kilde

25. maj 2018 Weekendavisen Sektion 4 (Ideer) Side 12 HENRIK PRÆTORIUS... 915 ord Id: e6c3730c

Data bekræfter: Styren kan give kræft

8. juni 2018 Jern Og Maskinindustrien Sektion 1 Side 34 Simon Dinsen Hansen ... 389 ord Id: e6c7d4c7

Skærpet advarsel: Styren er sandsynligvis kræftfremkaldende

29. maj 2018 Kemifokus.dk 265 ord Id: e6c4f1f0

Skærpet mistanke: Populær plastik kan 'sandsynligvis'give kræft

25. maj 2018 BT.dk Videnskab.dk... 283 ord Id: e6c3dbbd

Skærpet mistanke: Populær plastik kan 'sandsynligvis'give kræft Resumé

25. maj 2018 BT.dk / Plus (Abonnementsområde) 283 ord Id: e6c3daed

SKÆRPET MISTANKE TIL PLASTIC-KEMIKALIE

8. juni 2018 Søndagsavisen Vestsjælland Sektion 1 Side 7 58 ord Id: e6c7b604

Internationale medierTUC - Risks 852 - 9 June 2018

Trades Union Congress 7. juni 2018 3691 ord Id:e6c8b0bc

Chemical in packaging plastic, disposable cups could cause cancer - WHO

Daily Trust 5. juni 2018 Ojoma Akor... 496 ord Id:e6c7038c

Bao bì nhựa, cốc dùng một lần, cao su có thể gây ung thư cho người dùng

BaoveNTD 5. juni 2018 778 ord Id:e6c70386

Nguy cơ mắc bệnh ung thư từ việc sử dụng bao bì nhựa, cốc dùng một lần

Tap Chi Moi Truong 4. juni 2018 Huy Hoàng... 716 ord Id:e6c6ba2e

Common chemical used in plastic packaging ‘probably’ causes cancer.

Brinkwire 4. juni 2018 602 ord Id:e6c6a3e9

Bao bì nhựa, cốc dùng một lần có thể gây ung thư cho người dùng

Tin tức cập nhật liên tục 24/7 4. juni 2018 Theo Viet... 746 ord Id:e6c6a3e5

This plastic isn’t just harming wildlife anymore

Feeds Environmentguru 10. juli 2018 416 ord Id:e6d423ce

Bilag 1. Skriftlig videnskabelig formidling med peer review

Cancer Incidence in Workers Exposed to Styrene in the Danish-reinforced Plastics Industry, 1968–2012

Mette Skovgaard Christensen,[a,b] *Johnni Hansen,*[c] *Cecilia Høst Ramlau-Hansen,*[d] *Gunnar Toft,*[a,e] *and Henrik Kolstad*[a]

Background: Occupational exposure to styrene is widespread and has been suggested to be carcinogenic. The aim of this study was to investigate whether occupational exposure to styrene increases the risk of cancer, in particular lymphohematopoietic cancers.

Methods: We established a study population of 72,292 workers employed in 443 small and medium-sized companies producing reinforced plastics 1964–2007 by utilizing several national registries, expert assessment, and worker survey data. We identified incident cancer cases from 1968 to 2012 in the national Danish cancer registry and computed standardized incidence rate ratios (SIRs) with 95% confidence intervals (95% CI) based on national rates.

Results: Increasing SIRs of Hodgkin lymphoma, myeloid leukemia, and cancer of nasal cavities and sinuses were inconsistently associated with increasing duration of employment, early year of first employment, or styrene exposure probability. No such trends were observed for cancer of the esophagus, pancreas, lung, kidney, or urinary bladder, which have previously been associated with styrene exposure. Lung cancer showed an overall increased risk that decreased by duration of employment.

Conclusion: Occupational styrene exposure may be associated with Hodgkin lymphoma, myeloid leukemia, and cancer of nasal cavities and sinuses. Further studies are needed to evaluate if the observed associations are likely to be causal.

(*Epidemiology* 2017;28: 300–310)

Styrene is a viscous, organic solvent widely used in the production of resins that are incorporated into synthetic rubber, insulation, food containers, pipes, fiberglass reinforced plastics, and several other plastic products. Globally, the production of styrene has increased the past several decades, and styrene is one of the most frequently used chemicals.[1–3] In 2002, a working group convened by the International Agency for Research on Cancer (IARC) classified styrene as possibly carcinogenic to humans (group 2B) based on limited animal and epidemiologic evidence.[1] In 2011, The National Toxicology Program included styrene in the 12th Report on Carcinogens (RoC) as reasonably anticipated to be a human carcinogen, based on limited human evidence and sufficient evidence for carcinogenicity in animal studies along with supporting evidence from studies on mechanisms of carcinogenesis.[2] In 2014, this assessment was reviewed and the listing in RoC was maintained.[3]

In animal studies, increased incidence of benign and malignant lung tumors has been observed in mice following inhalation exposure to styrene[4] but not in rats by the same exposure route.[5] One inhalation study found increased incidence of mammary tumors among rats.[6] In one study of oral gavage exposure to styrene, an increase in the incidence of both benign and malignant lung tumors among mice was observed.[7]

Among workers in the styrene manufacturing industry, an excess mortality from lymphohematopoietic malignancies has been indicated.[8,9] However, these results may have been confounded in particular by exposure to benzene and other chemicals present in this industry.

In the styrene-butadiene rubber industry, increased mortality from leukemia and bladder, lung and laryngeal cancer has been observed.[10–12] However, these results are suspected to be related to exposure to 1,3-butadiene (an IARC group 1 carcinogen) rather than styrene.

High styrene exposure levels occur in the reinforced plastics industry where limited exposures to other human carcinogens are present.[2] This industry is therefore regarded an optimal setting for investigating possible health effects of styrene.[2,13]

In the reinforced plastics industry, increased occurrence has been shown for lung,[14–17] kidney,[16] bladder,[16,18] esophageal,[15,18] and pancreatic cancer,[16,19] as well as lymphohematopoietic malignancies.[20,21] However, no consistent trends by duration as a surrogate of exposure dose or level of exposure

Submitted 11 September 2015; accepted 28 November 2016.

From the [a]Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark; [b]Centre for Integrated Register-Based Research, CIRRAU, Aarhus University, Aarhus, Denmark; [c]Danish Cancer Society Research Centre, Copenhagen, Denmark; [d]Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark; and [e]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.

The study is funded by the Danish Working Environment Research Fund (Grant No.32-2011-09).

The authors report no conflicts of interest.

Data are available for replication through access to Statistics Denmark.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

Correspondence: Mette Skovgaard Christensen, Department of Occupational Medicine, Aarhus University Hospital, Norrebrogade 44, 2C, DK-8000 Aarhus C, Denmark. E-mail: Mette.S.Christensen@auh.rm.dk.

ISSN: 1044-3983/17/2802-0300
DOI: 10.1097/EDE.0000000000000608

have been observed. Most of these studies have used mortality as an outcome measure rather than cancer incidence.

In this study, we updated a large cohort of workers in the Danish-reinforced plastics industry, adding more than 20 years to follow-up.[15,19,20] The objective was to investigate whether occupational styrene exposure is followed by increased incidence of lymphohematopoietic malignancies, cancer of the esophagus, pancreas, lung, kidney, or urinary bladder. To demonstrate that styrene was associated with a particular cancer site, the association had to show consistent trends of increased risk with increasing duration of employment, early year of first employment, and exposure probability; these analyses were specified a priori. In addition, the large study population and long follow-up allowed us to screen a wide range of other cancer sites.

METHODS

Companies and Study Population

In the 1990s, a majority of all companies producing reinforced unsaturated polyester in Denmark between 1964 and 1988 and all their employees were identified through several national registries. Detailed information is found in previous publications.[15,19,20] In 2012, the original data were updated from various sources. The Danish Working Environment Authority provided information on reinforced plastics companies active between 1993 and 2010, and the Danish National Central Business Register delivered information on reinforced plastics companies still active. This company list was then reviewed independently by three dealers of plastic raw materials with thorough knowledge of the industry during the past four decades. They supplied information on production characteristics and years of relevant production. Adding information from the original 386 companies from the previous study, we ended up with an updated list of 469 companies identified by unique company identification numbers with specification of first and last year of relevant production.

Employees in these companies since 1964 and alive as of 2 April 1968 were obtained from the Danish Supplementary Pension Fund Register. In Denmark, it has been mandatory since 1964 for employers to make payments to this fund on behalf of employees and payments are automatically drawn from the employee's gross salary. It is a unique register for retrieval of employees, identified by their personal identification number in companies by use of the company identification number.[22]

Information on employees was obtained from the Supplementary Pension Fund Register at four occasions: In 1988, 1998, 2007, and 2013 (in 2013, the dataset update covered the years 1964–2000). In 2001, the Supplementary Pension Fund reorganized their data and deleted persons deceased for at least 5 years. For workers identified in the Supplementary Pension Fund Register after 2001 (n = 24,520), this obliged us to restrict the follow-up period for this subcohort to begin at the earliest in 1997 (5 years before 2001).

We excluded companies for which we were not able to assign an exposure probability estimate as defined later (17 companies employing a total of 70 workers). We also excluded companies with an estimated exposure probability of 0% for all years of follow-up (9 companies; 209 workers). The data then consisted of 443 companies, employing a total of 73,969 workers between 1964 and 2007.

The Danish Civil Registration System contains information on all persons living in Denmark since 2 April 1968. All residents are assigned a unique 10-digit personal identification number at birth or upon later residence or tax-paying in Denmark. The unique number enables accurate linkage between all national registers.[23] From this register, we obtained information on sex, date of birth, death, emigration, or disappearance. We excluded persons living in Greenland (n = 232). For persons identified after 2001 (n = 24,520), we excluded those censored before the restricted start of follow-up (n = 1,445). The final cohort eligible for analyses compromised 60,478 men and 11,774 women, a total of 72,292 individuals.

Person-years at Risk

Person-years at risk were accumulated at the earliest from 2 April 1968 when the Civil Registration System was established, or from the 1 January the year of first employment, which ever was later. For persons identified after 2001 (n = 24,520), person-years at risk were accumulated from 1 January 1997 or the date of first employment if later. Accumulation of person-years at risk ended at 31 December 2012, the date of death, emigration, or disappearance, whichever came first.

Follow-up for Cancers

We identified cases of cancer, except nonmelanoma skin cancers, in the Danish Cancer Registry. In Denmark, all cancers have been registered in this registry since 1943, and it has been mandatory for physicians and hospitals to report cases of cancer since 1987. Cancer diagnoses in the Danish Cancer Register are classified according to ICD-7 (1943–1977), ICD-O (1978–2003), and ICD-10 (2004 and onwards).[24]

Statistical Methods

We applied national site-specific cancer incidence rates by sex, 5-year age groups, and 5-year calendar periods to the person-years under observation to obtain the expected number of cancers in the study population, had the cohort experienced the same rate of cancers as that observed in the general population. We computed standardized incidence rate ratios (SIRs) as the ratio of the observed and the expected numbers, with 95% confidence intervals (95% CI), assuming a Poisson distribution.

We performed analyses based on duration of employment, year of first employment, and styrene exposure probability. All analyses were also performed including 10 years of latency.

To indirectly identify potential confounding from tobacco smoking, we calculated combined standardized

incidence rate ratios for cancers that are generally accepted to be related to smoking except lung cancer (cancer of the buccal cavity and pharynx, esophagus, stomach, colon, rectum, liver, pancreas, nasal cavity and sinuses, larynx, uterine cervix, ovary, kidney, renal pelvis and ureter, urinary bladder, and myeloid leukemia)[25] as suggested by Steenland et al.[26] We also applied the method outlined by Axelson.[27] Analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC).

Worker Survey

In 2013, we conducted a survey among a random sample of workers from each company with the aim of classifying each company by the fraction of styrene-exposed workers because we had no access to job title or job task indicating individual styrene exposure. The survey included a random sample of workers from each company that was stratified by decade of employment and gender. From companies with 1–99, 100–499, and 500 or more employees within each of these strata, we applied sampling fractions of 55%, 25%, and 10%, respectively. A total of 23,808 workers were sampled. We excluded workers deceased, lost to follow-up, emigrated, or living in Greenland (n = 5,832). We also excluded those who were registered as protected against inquiries in connection with scientific studies in the Civil Registration System (n = 2,433) or persons above 79 years of age at 1 November 2013 (n = 436). A total of 15,107 workers remained after these exclusions and they were mailed a short questionnaire about their work in the reinforced plastics industry, and 11,493 workers responded (76%) of whom 8,621 were men and 2,872 were women.

We supplemented the survey with information from a comparable survey conducted in 2000 among a small subsample of workers (n = 465) in some of the companies.[28] Based on this information, we for each company estimated the proportion of exposed respondents within each decade, simply by dividing the number who had confirmed working with molding fiberglass-reinforced polyester by number of respondents. These estimates classified each company and subsequently the employees according to exposure probability for each decade. We grouped styrene exposure probabilities into low (1%–24% probability of exposure), low-medium (25%–49% probability of exposure), medium-high (50%–74% probability of exposure), and high (75%–100% probability of exposure).

Smoking Survey

In the 2013 survey, the 7,368 workers who recalled employment in the industry were also asked for smoking habits over the years. We tabulated smoking status (never vs. ever smoker) by duration and first year of employment and styrene exposure probability, and calculated odds ratios of ever smoking for the different proxies of exposure. To evaluate differential participation, we investigated the association between duration of employment, year of first employment, and participation in the survey among the 23,808 workers randomly sampled for the survey.

The Danish Data Protection Agency approved the study (j.no: 1-16-02-01-07). In Denmark, register studies and individual surveys, where biological materials are not included, do not need approval from the Committee System on Biomedical Research Ethics. Participants in the survey were informed of the possibility to withdraw their consent of participation at any point in time.

RESULTS

The total cohort of 72,292 workers employed in 443 companies accumulated a total of 1,686,342 person-years, and we identified 8,961 incident cases of cancer.

The standardized incidence rate ratio (SIR) for all cancers was 1.04 (95% CI, 1.01, 1.06) both sexes combined. By including a 10-year lag period, the SIR remained 1.04 (1.02–1.06). Table 1 presents the SIR values for all cancer sites including stratified by sex and combined for both sexes.

We observed increased rate ratios for cancer of the mouth, pharynx, nasal cavities and sinuses, larynx, lung, bronchus and trachea, and mesothelioma. We observed decreased rate ratios for small intestine, skin melanomas, cancer of the prostate, and multiple myeloma. No obvious sex or exposure lag differences were observed.

Tables 2–4 present the SIRs for cancer sites associated with styrene exposure in previous studies or showing estimates in Table 1 with a 2.5% lower confidence interval above or a 97.5% upper confidence interval below 1.00 for both genders combined and with no exposure lagging.

For Hodgkin lymphoma and myeloid leukemia, we observed increased rate ratios associated with increased duration of employment. For nasal cavities and sinuses and melanoma of skin, increased rate ratios were inconsistently associated with increased duration of employment (Table 2). For cancer of larynx and lung, we observed some evidence of decreasing rate ratios by increasing duration of employment, although the highest SIR value was seen among workers with 1–4 years of employment (Table 2). No such associations by duration of employment were evident for the other cancer sites.

Workers first employed in the 1960s showed a doubled risk of Hodgkin's lymphoma while those first employed in later years showed consistently lower risks (Table 3). For the other sites, there were no obvious associations of increasing rate ratio with earlier first employment.

For cancer of the mouth, nasal cavities, and sinuses, Hodgkin lymphoma, and myeloid leukemia, we observed the highest rate ratios for the two highest exposure probability categories (Table 4). Such patterns were not seen for the other cancer sites. Decreased risk of lung cancer was inconsistently associated with increased exposure probability.

All tobacco-associated cancers except lung cancer amounted to 3,579 cases corresponding with an overall SIR of 1.05 (95% CI, 1.02, 1.09). Analyses by duration of employment,

TABLE 1. SIRs and 95% CIs for Cancer by Gender and Both Gender Combined with No Lag and a 10-year Lag, 72,292 Workers of the Danish-reinforced Plastics Industry, 1968–2007

	Gender				Genders Combined			
	Men		Women		No Lag		10 Years Lag	
	1,412,790 Person-years		273,552 Person-years		1,686,342 Person-years		1,088,431 Person-years	
Cancer Site (ICD 10th Revision[a])	**Cases Observed**	**SIR (95% CI)**	**Cases Observed**	**SIR (95% CI)**	**Cases Observed**	**SIR (95% CI)**	**Cases Observed**	**SIR (95% CI)**
All cancers	7,560	1.04 (1.02, 1.06)	1,401	1.02 (0.97, 1.08)	8,961	1.04 (1.01, 1.06)	7,760	1.04 (1.02, 1.06)
Buccal cavity and pharynx (C00–C14)	376	1.21(1.09, 1.34)	22	0.99 (0.62, 1.50)	398	1.20 (1.08, 1.32)	351	1.23 (1.11, 1.37)
Lip (C00)	37	1.02 (0.72, 1.40)	0	0.00 (0.00, 3.00)	37	0.98 (0.69, 1.36)	29	1.02 (0.69, 1.47)
Tongue (C01–02)	60	1.23 (0.93, 1.58)	5	1.31 (0.42, 3.06)	65	1.23 (0.95, 1.57)	61	1.33 (1.01, 1.70)
Mouth (C03–06)	100	1.30 (1.06, 1.58)	5	0.72 (0.23, 1.69)	105	1.25 (1.03, 1.52)	92	1.27 (1.02, 1.55)
Salivary glands (C07–08)	17	1.10 (0.64, 1.77)	4	1.78 (0.48, 4.55)	21	1.19 (0.74, 1.82)	20	1.38 (0.84, 2.13)
Pharynx (C09–13)	162	1.22 (1.04, 1.42)	8	1.00 (0.43, 1.97)	170	1.21 (1.03, 1.40)	149	1.21 (1.02, 1.42)
Digestive organs (C15–26)	1,643	0.98 (0.94, 1.03)	221	1.05 (0.92, 1.20)	1,864	0.99 (0.95, 1.04)	1,658	1.00 (0.95, 1.05)
Esophagus (C15)	152	1.05 (0.89, 1.23)	8	0.98 (0.42, 1.92)	160	1.05 (0.89, 1.22)	143	1.05 (0.88, 1.23)
Stomach (C16)	213	1.08 (0.94, 1.23)	24	1.53 (0.98, 2.27)	237	1.11 (0.97, 1.26)	205	1.15 (1.00, 1.32)
Small intestine (C17)	15	0.64 (0.36, 1.06)	0	0.00 (0.00, 1.05)	15	0.56 (0.31, 0.92)	15	0.60 (0.33, 1.01)
Colon incl recto-sigmoideum (C19–18)	545	0.97 (0.89, 1.05)	92	1.02 (0.82, 1.25)	637	0.98 (0.90, 1.06)	578	0.99 (0.91, 1.08)
Rectum (C20)	347	0.92 (0.82, 1.02)	44	1.09 (0.79, 1.47)	391	0.94 (0.84, 1.03)	345	0.94 (0.84, 1.05)
Liver (C22)	100	1.02 (0.83, 1.24)	5	0.66 (0.21, 1.55)	105	1.00 (0.82, 1.21)	95	1.02 (0.82, 1.24)
Gallbladder and biliary tract (C23–24)	33	0.86 (0.59, 1.20)	12	1.54 (0.80, 2.69)	45	0.97 (0.71, 1.30)	37	0.91 (0.64, 1.26)
Pancreas (C25)	214	1.03 (0.90, 1.18)	33	1.11 (0.76, 1.56)	247	1.04 (0.91, 1.18)	217	1.04 (0.91, 1.19)
Anus, other and unspecified digestive organs (C21 + C26)	24	1.14 (0.73, 1.70)	<4	0.42 (0.08, 1.23)	27	0.96 (0.63, 1.40)	24	0.97 (0.62, 1.44)
Respiratory system and intrathoracic organs (C30–39)	1,650	1.28 (1.21, 1.34)	218	1.40 (1.22, 1.60)	1,868	1.29 (1.23, 1.35)	1,637	1.30 (1.24, 1.37)
Nasal cavities and sinuses (C30–31)	38	1.69 (1.20, 2.33)	<4	0.88 (0.10, 3.18)	40	1.62 (1.16, 2.21)	34	1.62 (1.12, 2.26)
Larynx (C32)	166	1.31 (1.12, 1.52)	10	2.12 (1.02, 3.91)	176	1.34 (1.15, 1.55)	149	1.33 (1.13, 1.57)
Lung, bronchus and trachea (C33–34)	1,433	1.26 (1.20, 1.33)	205	1.39 (1.21, 1.60)	1,638	1.28 (1.22, 1.34)	1,446	1.30 (1.23, 1.37)
Thymus (C37)	<4	1.28 (0.26, 3.73)	<4	2.79 (0.04, 15.5)	4	1.48 (0.40, 3.78)	<4	0.49 (0.01, 2.70)
Heart and mediastinum (C38)	6	1.22 (0.45, 2.65)	0	0.00 (0.00, 5.46)	6	1.07 (0.39, 2.33)	5	1.20 (0.39, 2.81)
Pleura (C38.4)	4	1.56 (0.42, 4.00)	0	0.00 (0.00, 25.0)	4	1.48 (0.40, 3.78)	<4	0.93 (0.10, 3.35)
Bones, joints and articular cartilage (C40–41)	12	0.85 (0.44, 1.48)	4	2.15 (0.58, 5.50)	16	1.00 (0.57, 1.62)	14	1.30 (0.71, 2.19)
Skin (C43–44)	1,917	0.82 (0.78, 0.86)	419	0.93 (0.85, 1.03)	2,336	0.84 (0.80, 0.87)	2,099	0.85 (0.82, 0.89)
Melanoma of skin (C43)	265	0.81 (0.71, 0.91)	63	0.82 (0.63, 1.04)	328	0.81 (0.72, 0.90)	275	0.83 (0.73, 0.93)
Other skin (C44)	1,652	0.82 (0.78, 0.86)	356	0.96 (0.86, 1.06)	2,008	0.84 (0.81, 0.88)	1,824	0.86 (0.82, 0.90)
Mesothelium and connective tissue (C45–49)	170	1.59 (1.36, 1.84)	12	0.96 (0.50, 1.68)	182	1.52 (1.31, 1.76)	155	1.56 (1.32, 1.82)
Mesothelium (C45)	110	2.60 (2.14, 3.13)	0	0.00 (0.00, 2.38)	110	2.51 (2.06, 3.02)	97	2.49 (2.02, 3.04)
Peripheral nerves and autonomic nervous system (C47)	<4	0.38 (0.00, 2.13)	0	0.00 (0.00, 8.06)	<4	0.33 (0.00, 1.81)	0	0.00 (0.00, 2.03)
Peritoneum and retroperitoneum (C48)	11	1.03 (0.52, 1.85)	<4	0.77 (0.09, 2.78)	13	0.98 (0.52, 1.68)	10	0.97 (0.47, 1.79)
Other connective tissue (C49)	48	0.93 (0.69, 1.23)	10	1.27 (0.61, 2.34)	58	0.97 (0.74, 1.26)	48	0.99 (0.73, 1.31)
Breast (C50)	10	0.79 (0.38, 1.45)	422	0.96 (0.87, 1.05)	432	0.95 (0.86, 1.05)	359	0.93 (0.84, 1.04)
Female genital organs (C51–58)	-	-	184	0.93 (0.80, 1.08)	-	-	139	0.89 (0.75, 1.05)
External female genital organs and vagina (C51–52)	-	-	7	0.77 (0.31, 1.58)	-	-	4	0.51 (0.14, 1.32)
Cervix uteri (C53)	-	-	67	1.11 (0.86, 1.41)	-	-	45	1.13 (0.83, 1.52)
Corpus uteri (C54–55)	-	-	54	0.82 (0.62, 1.07)	-	-	46	0.80 (0.59, 1.07)

(*Continued*)

TABLE 1. (*Continued*)

Cancer Site (ICD 10th Revision[a])	Gender				Genders Combined			
	Men		Women		No Lag		10 Years Lag	
	1,412,790 Person-years		273,552 Person-years		1,686,342 Person-years		1,088,431 Person-years	
	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)
Ovary, fallopian tube, and broad ligament (C56)	-	-	55	0.90 (0.68, 1.17)	-	-	43	0.85 (0.61, 1.14)
Other and unspecified female genital organs (C57)	-	-	<4	1.17 (0.02, 6.52)	-	-	<4	1.31 (0.02, 7.28)
Male genital organs (C61–63)	1,307	0.89 (0.85, 0.94)	-	-	-	-	1,144	0.88 (0.83, 0.93)
Prostate (C61)	1,099	0.88 (0.83, 0.94)	-	-	-	-	1,025	0.88 (0.82, 0.93)
Testis (C62)	181	0.95 (0.81, 1.10)	-	-	-	-	96	0.89 (0.72, 1.09)
Other and unspecified male genital organs (C63)	27	0.96 (0.64, 1.40)	-	-	-	-	23	0.96 (0.61, 1.43)
Urinary tract (C64–68)	927	1.07 (1.00, 1.14)	47	0.83 (0.61, 1.10)	974	1.05 (0.99, 1.12)	861	1.07 (1.00, 1.14)
Kidney (C64)	226	1.12 (0.98, 1.27)	21	1.13 (0.70, 1.73)	247	1.12 (0.98, 1.27)	218	1.15 (1.00, 1.31)
Renal pelvis and ureter (C65–66)	41	0.78 (0.56, 1.05)	<4	0.41 (0.05, 1.48)	43	0.75 (0.54, 1.01)	41	0.81 (0.58, 1.11)
Urinary bladder (C67)	651	1.08 (1.00, 1.16)	24	0.74 (0.47, 1.10)	675	1.06 (0.98, 1.14)	593	1.06 (0.98, 1.15)
Other and unspecified urinary organs (C68)	9	1.16 (0.53, 2.20)	0	0.00 (0.00, 5.21)	9	1.06 (0.48, 2.01)	9	1.18 (0.54, 2.24)
Eye, brain, and other parts of central nervous system (C69–72)	325	0.97 (0.87, 1.08)	68	0.99 (0.77, 1.26)	393	0.97 (0.88, 1.07)	305	0.94 (0.84, 1.05)
Eye (C69)	15	0.67 (0.38, 1.11)	<4	0.28 (0.00, 1.58)	16	0.62 (0.35, 1.01)	11	0.52 (0.26, 0.94)
Meninges (C70)	38	0.83 (0.59, 1.15)	24	1.07 (0.68, 1.59)	62	0.91 (0.70, 1.17)	52	0.91 (0.68, 1.20)
Brain (C71)	224	1.02 (0.89, 1.16)	32	0.97 (0.66, 1.36)	256	1.01 (0.89, 1.14)	197	0.99 (0.85, 1.13)
Spinal cord, cranial nerves, and unsp. part of CNS (C72)	48	1.00 (0.74, 1.32)	11	1.19 (0.59, 2.12)	59	1.03 (0.78, 1.33)	45	0.96 (0.70, 1.28)
Endocrine glands (C73–75)	41	1.26 (0.91, 1.71)	15	1.03 (0.58, 1.70)	56	1.19 (0.90, 1.54)	45	1.24 (0.90, 1.66)
Thyroid gland (C73)	34	1.22 (0.84, 1.70)	13	0.95 (0.50, 1.62)	47	1.13 (0.83, 1.50)	39	1.21 (0.86, 1.66)
Adrenal gland (C74)	7	1.87 (0.75, 3.85)	<4	2.98 (0.33, 10.8)	9	2.04 (0.93, 3.87)	6	1.74 (0.64, 3.79)
Lymphatic and hematopoietic tissue (C81–96)	585	0.96 (0.89, 1.04)	76	1.01 (0.79, 1.26)	661	0.97 (0.90, 1.04)	547	0.96 (0.88, 1.04)
Hodgkin lymphoma (C81)	57	1.20 (0.91, 1.56)	7	1.24 (0.50, 2.56)	64	1.21 (0.93, 1.54)	40	1.22 (0.87, 1.67)
Non-Hodgkin lymphoma (C82–85)	242	0.99 (0.87, 1.12)	28	0.85 (0.56, 1.22)	270	0.97 (0.86, 1.10)	221	0.94 (0.82, 1.07)
Multiple myeloma (C90)	79	0.78 (0.61, 0.97)	11	0.92 (0.46, 1.65)	90	0.79 (0.64, 0.97)	78	0.77 (0.61, 0.96)
Lymphatic leukemia (C91)	108	0.92 (0.76, 1.11)	15	1.27 (0.71, 2.10)	123	0.96 (0.79, 1.14)	108	0.96 (0.79, 1.16)
Myeloid leukemia (C92)	87	1.03 (0.83, 1.28)	14	1.22 (0.67, 2.05)	101	1.06 (0.86, 1.28)	88	1.13 (0.91, 1.39)
Monocytic leukemia (C93)	<4	0.85 (0.17, 2.49)	0	0.00 (0.00, 9.65)	<4	0.77 (0.15, 2.25)	<4	0.56 (0.06, 2.03)
Other and unspec. leukemia (C94–96)	9	1.07 (0.49, 2.02)	<4	0.96 (0.01, 5.34)	10	1.05 (0.50, 1.94)	10	1.26 (0.60, 2.31)
Ill-defined and unspecified cancer (C76–80)	249	1.07 (0.94, 1.21)	49	1.23 (0.91, 1.63)	298	1.10 (0.98, 1.23)	270	1.12 (0.99, 1.26)

[a]Diagnoses were coded according to the ICD revision in force at time of diagnosis.

year of first employment, and styrene exposure probability showed no consistent association or no trend patterns (not tabulated).

The prevalence of male smokers in the Danish population 1986–1987 was 49% among the general population, 54% among skilled and unskilled blue-collar workers, and 46% among white-collar workers.[29] Using Axelson's method assuming that ¾ of the study population were male skilled or unskilled blue-collar workers and ¼ were male white-collar workers, and that smokers had a 10-fold increased risk of lung cancer, an increased rate ratio of 1.04 for lung cancer solely due to smoking was expected for the total study population (not tabulated).

TABLE 2. SIRs and 95% CIs for Selected Cancer Sites by Duration of Employment, 72,292 Workers of the Danish-reinforced Plastics Industry, 1968–2007

	Duration of Employment (Years)							
	<1		1–4		5–9		≥10	
	699,306 Person-years		600,790 Person-years		216,858 Person-years		169,293 Person-years	
Cancer Site (ICD 10th Revision[a])	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)
All cancers	2,893	0.91 (0.88, 0.95)	3,392	1.16 (1.13, 1.20)	1,266	1.00 (0.95, 1.06)	1,410	1.08 (1.02, 1.14)
Mouth (C03–06)	33	1.01 (0.69, 1.42)	49	1.71 (1.27, 2.26)	13	1.13 (0.60, 1.93)	10	0.92 (0.44, 1.69)
Pharynx (C09–13)	66	1.17 (0.91, 1.49)	64	1.32 (1.01, 1.68)	28	1.47 (0.98, 2.13)	12	0.71 (0.37, 1.25)
Esophagus (C15)	60	1.06 (0.81, 1.36)	59	1.17 (0.89, 1.50)	14	0.64 (0.35, 1.08)	27	1.16 (0.76, 1.68)
Small intestine (C17)	6	0.61 (0.22, 1.32)	4	0.44 (0.12, 1.13)	<4	0.77 (0.15, 2.24)	<4	0.51 (0.06, 1.82)
Pancreas (C25)	90	1.06 (0.85, 1.30)	82	1.04 (0.82, 1.29)	39	1.09 (0.78, 1.49)	36	0.96 (0.67, 1.33)
Nasal cavities and sinuses (C30–31)	9	0.98 (0.45, 1.86)	15	1.81 (1.01, 2.98)	10	2.80 (1.34, 5.16)	6	1.65 (0.60, 3.58)
Larynx (C32)	74	1.51 (1.19, 1.90)	67	1.53 (1.19, 1.94)	20	1.06 (0.64, 1.63)	15	0.76 (0.42, 1.25)
Lung, bronchus and trachea (C33–34)	561	1.24 (1.14, 1.35)	648	1.53 (1.42, 1.66)	215	1.11 (0.97, 1.27)	214	1.01 (0.88, 1.15)
Melanoma of skin (C43)	92	0.58 (0.46, 0.71)	141	0.99 (0.84, 1.17)	39	0.71 (0.50, 0.96)	56	1.16 (0.87, 1.50)
Mesothelioma (C45)	43	2.67 (1.93, 3.59)	32	2.22 (1.52, 3.13)	13	2.06 (1.10, 3.52)	22	3.14 (1.97, 4.75)
Prostate (C61)[b]	340	0.77 (0.69, 0.86)	372	0.93 (0.84, 1.03)	162	0.87 (0.74, 1.02)	225	1.04 (0.91, 1.18)
Kidney (C64)	80	0.97 (0.77, 1.21)	92	1.24 (1.00, 1.52)	33	1.03 (0.71, 1.45)	42	1.31 (0.94, 1.77)
Urinary bladder (C67)	347	1.03 (0.93, 1.15)	169	1.19 (1.02, 1.38)	110	1.11 (0.91, 1.34)	49	0.84 (0.62, 1.11)
Hodgkin lymphoma (C81)	22	1.00 (0.63, 1.52)	21	1.12 (0.70, 1.72)	10	1.46 (0.70, 2.68)	11	1.98 (0.99, 3.54)
Non-Hodgkin lymphoma (C82–85)	86	0.81 (0.65, 1.00)	110	1.17 (0.96, 1.41)	31	0.80 (0.54, 1.13)	43	1.12 (0.81, 1.51)
Multiple myeloma (C90)	31	0.76 (0.51, 1.07)	27	0.72 (0.47, 1.04)	19	1.13 (0.68, 1.77)	13	0.72 (0.38, 1.22)
Lymphatic leukemia (C91)	42	0.90 (0.65, 1.21)	44	1.03 (0.75, 1.38)	9	0.47 (0.22, 0.90)	28	1.38 (0.92, 2.00)
Myeloid leukemia (C92)	31	0.87 (0.59, 1.24)	33	1.03 (0.71, 1.44)	15	1.08 (0.61, 1.79)	22	1.56 (0.98, 2.36)

[a]Diagnoses were coded according to the ICD revision in force at time of diagnosis.
[b]Males only

Table 5 displays slightly lower prevalence of ever smokers with longer duration of employment and later first year of employment among the 7,368 respondents of the smoking survey. Decreasing odds of smoking were observed both with increasing duration of employment and later year of first employment. No difference in smoking prevalence was evident between the different styrene exposure probability groups.

Participation in the smoking survey increased by duration and later first year of employment (*P* values for trend <0.01). Workers with more than 10 years of employment were four times more likely to participate than workers with less than 1 year of employment (OR, 4.03 [95% CI, 3.67, 4.42]). Workers first employed in the 2000s had a five-fold increased odds of participating than workers first employed in the 1960s (OR, 5.84 [95% CI, 5.06, 6.75]; not tabulated).

eTable A (http://links.lww.com/EDE/B149) displays the distribution of companies and workers by styrene exposure probability and company size. Company size was estimated as the mean number of positions at a given point in time. Overall, 68% of the companies were small workshops with fewer than 10 positions, and 55% of the study population was employed in companies with fewer than 100 positions. Among companies with a high exposure probability, 99% were small workshops with fewer than 50 positions employing 48% of the workers of this category. Among companies with a low exposure probability, 63% had fewer than 50 positions and employed 16% of the workers in this category.

DISCUSSION

Overall analyses suggested higher risk of cancer of the mouth, pharynx, nasal cavities and sinuses, larynx, lung, bronchus, trachea, and mesothelioma. We observed slightly lower risks for cancer of the small intestine, melanoma of skin, prostate cancer, and multiple myeloma. Analyses by duration and first year of employment and by the probability of being exposed to styrene indicated increasing risks of Hodgkin lymphoma, myeloid leukemia, and cancer of nasal cavities and sinuses by some of these proxy measures of styrene exposure, and a decreasing risk of lung cancer by duration of employment.

Our a priori-specified criterion for an association with styrene exposure was increasing occurrence of cancer at a given site with duration of employment, early year of first employment, and exposure probability. No cancer

TABLE 3. SIRs and 95% CIs for Selected Cancer Sites by Year of First Employment in a Reinforced Plastics Company, 72,292 Workers of the Danish-reinforced Plastics Industry, 1968–2007

	Year of First Employment									
	1964–1969		1970–1979		1980–1989		1990–1999		2000–2007	
	273,896 Person-years		664,528 Person-years		478,260 Person-years		175,769 Person-years		93,794 Person-years	
Cancer Site (ICD 10th Revision[a])	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)
All cancers	2,372	1.03 (0.99, 1.07)	3,764	1.03 (1.00, 1.06)	2,030	1.07 (1.02, 1.11)	496	1.03 (0.94, 1.12)	299	1.01 (0.90, 1.13)
Mouth (C03–06)	16	0.86 (0.49, 1.40)	45	1.24 (0.91, 1.66)	29	1.42 (0.95, 2.04)	11	2.13 (1.06, 3.82)	4	1.16 (0.31, 2.98)
Pharynx (C09–13)	29	1.07 (0.72, 1.54)	70	1.16 (0.90, 1.46)	48	1.34 (0.99, 1.78)	12	1.21 (0.63, 2.12)	11	1.47 (0.73, 2.64)
Esophagus (C15)	43	1.07 (0.77, 1.44)	75	1.15 (0.90, 1.44)	29	0.85 (0.57, 1.22)	9	1.17 (0.54, 2.23)	4	0.79 (0.21, 2.01)
Small intestine (C17)	<4	0.14 (0.00, 0.78)	8	0.70 (0.30, 1.38)	5	0.85 (0.28, 1.99)	0	0.00 (0.00, 2.46)	<4	1.02 (0.01, 5.66)
Pancreas (C25)	77	1.11 (0.87, 1.38)	99	0.97 (0.79, 1.18)	53	1.09 (0.81, 1.42)	15	1.38 (0.77, 2.28)	<4	0.44 (0.09, 1.29)
Nasal cavities and sinuses (C30–31)	8	1.25 (0.54, 2.46)	21	2.01 (1.24, 3.07)	8	1.46 (0.63, 2.88)	<4	2.14 (0.43, 6.25)	0	0.00 (0.00, 4.01)
Larynx (C32)	43	1.20 (0.87, 1.62)	82	1.43 (1.14, 1.77)	35	1.23 (0.86, 1.72)	8	1.31 (0.56, 2.58)	8	2.00 (0.86, 3.95)
Lung (C33–34)	471	1.21 (1.10, 1.32)	703	1.26 (1.17, 1.36)	360	1.42 (1.27, 1.57)	68	1.34 (1.04, 1.69)	36	1.21 (0.84, 1.67)
Melanoma of skin (C43)	60	0.78 (0.60, 1.00)	125	0.79 (0.66, 0.94)	97	0.90 (0.73, 1.10)	27	0.71 (0.47, 1.04)	19	0.77 (0.46, 1.20)
Mesothelium (C45)	39	3.11 (2.21, 4.25)	25	1.34 (0.87, 1.98)	43	4.52 (3.27, 6.08)	0	0.00 (0.00, 1.89)	<4	2.55 (0.51, 7.46)
Prostate (C61)[b]	331	0.87 (0.78, 0.97)	439	0.85 (0.77, 0.93)	249	0.96 (0.84, 1.09)	49	0.93 (0.69, 1.23)	31	0.86 (0.58, 1.22)
Kidney (C64)	52	0.92 (0.68, 1.20)	114	1.21 (1.00, 1.46)	56	1.13 (0.85, 1.47)	15	1.22 (0.68, 2.00)	10	1.18 (0.56, 2.17)
Urinary bladder (C67)	215	1.10 (0.96, 1.26)	275	1.01 (0.89, 1.13)	155	1.21 (1.03, 1.42)	16	0.65 (0.37, 1.06)	14	0.96 (0.52, 1.60)
Hodgkin lymphoma (C81)	20	2.12 (1.29, 3.27)	17	0.82 (0.48, 1.32)	16	1.07 (0.61, 1.73)	8	1.52 (0.65, 2.99)	<4	1.10 (0.22, 3.22)
Non-Hodgkin lymphoma (C82–85)	53	0.81 (0.61, 1.06)	131	1.12 (0.94, 1.33)	56	0.84 (0.63, 1.09)	17	0.97 (0.56, 1.55)	13	1.21 (0.64, 2.06)
Multiple myeloma (C90)	18	0.56 (0.33, 0.88)	50	1.03 (0.77, 1.36)	17	0.70 (0.41, 1.12)	<4	0.57 (0.11, 1.66)	<4	0.60 (0.07, 2.16)
Lymphatic leukemia (C91)	32	0.89 (0.61, 1.25)	56	1.02 (0.77, 1.32)	25	0.91 (0.59, 1.34)	<4	0.31 (0.04, 1.14)	8	2.03 (0.87, 4.00)
Myeloid leukemia (C92)	26	1.05 (0.68, 1.53)	46	1.13 (0.83, 1.51)	24	1.13 (0.72, 1.68)	<4	0.53 (0.11, 1.54)	<4	0.62 (0.07, 2.24)

[a]Diagnoses were coded according to the ICD revision in force at time of diagnosis.
[b]Males only.

TABLE 4. SIRs and 95% CIs for Selected Cancer Sites by Styrene Exposure Probability, 72,292 Workers of the Danish-reinforced Plastics Industry, 1968–2007

	Probability of Direct Exposure							
	Low		Lower Medium		Upper Medium		High	
	727,943 Person-years		374,687 Person-years		311,981 Person-years		271,637 Person-years	
Cancer Site (ICD 10th Revision[a])	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)	Cases Observed	SIR (95% CI)
All cancers	4,590	1.05 (1.02, 1.08)	2,063	1.04 (1.00, 1.09)	1,371	0.99 (0.94, 1.05)	937	1.01 (0.95, 1.08)
Mouth (C03–06)	41	0.99 (0.71, 1.34)	21	1.13 (0.70, 1.73)	32	2.29 (1.57, 3.23)	11	1.12 (0.56, 2.00)
Pharynx (C09–13)	84	1.23 (0.98, 1.52)	34	1.13 (0.78, 1.57)	26	1.08 (0.71, 1.59)	26	1.45 (0.95, 2.12)
Esophagus (C15)	83	1.05 (0.84, 1.30)	34	1.02 (0.71, 1.43)	26	1.06 (0.69, 1.56)	17	1.08 (0.63, 1.72)
Small intestine (C17)	9	0.66 (0.30, 1.26)	<4	0.49 (0.10, 1.44)	<4	0.23 (0.00, 1.30)	<4	0.69 (0.08, 2.50)
Pancreas (C25)	120	0.97 (0.81, 1.16)	62	1.14 (0.87, 1.46)	39	1.06 (0.75, 1.44)	26	1.13 (0.74, 1.66)
Nasal cavities and sinuses (C30–31)	15	1.21 (0.68, 1.99)	9	1.63 (0.74, 3.09)	11	2.73 (1.36, 4.90)	5	1.84 (0.59, 4.28)
Larynx (C32)	84	1.24 (0.99, 1.54)	49	1.66 (1.23, 2.20)	26	1.22 (0.80, 1.79)	17	1.27 (0.74, 2.03)
Lung, bronchus and trachea (C33–34)	905	1.35 (1.27, 1.45)	372	1.25 (1.13, 1.38)	236	1.19 (1.04, 1.35)	125	1.07 (0.89, 1.27)
Melanoma of skin (C43)	143	0.76 (0.64, 0.89)	83	0.93 (0.74, 1.15)	56	0.80 (0.61, 1.04)	46	0.79 (0.58, 1.05)
Mesothelioma (C45)	82	3.55 (2.82, 4.40)	13	1.35 (0.72, 2.32)	10	1.45 (0.69, 2.66)	5	1.18 (0.38, 2.76)
Prostate (C61)[b]	616	0.91 (0.84, 0.98)	221	0.85 (0.74, 0.97)	150	0.79 (0.67, 0.92)	112	0.98 (0.80, 1.18)
Kidney (C64)	130	1.16 (0.97, 1.38)	51	1.04 (0.77, 1.36)	33	0.92 (0.63, 1.29)	33	1.36 (0.93, 1.91)
Urinary bladder (C67)	347	1.03 (0.93, 1.15)	169	1.19 (1.02, 1.38)	110	1.11 (0.91, 1.34)	49	0.84 (0.62, 1.11)
Hodgkin lymphoma (C81)	27	1.16 (0.77, 1.69)	14	1.21 (0.66, 2.02)	9	0.92 (0.42, 1.74)	14	1.67 (0.91, 2.80)
Non-Hodgkin lymphoma (C82–85)	121	0.89 (0.73, 1.06)	68	1.10 (0.85, 1.39)	52	1.13 (0.84, 1.48)	29	0.89 (0.59, 1.28)
Multiple myeloma (C90)	47	0.80 (0.58, 1.06)	16	0.63 (0.36, 1.02)	15	0.84 (0.47, 1.39)	12	1.08 (0.55, 1.88)
Lymphatic leukemia (C91)	70	1.06 (0.82, 1.33)	28	0.97 (0.64, 1.40)	15	0.73 (0.41, 1.21)	10	0.76 (0.37, 1.40)
Myeloid leukemia (C92)	46	0.97 (0.71, 1.30)	25	1.15 (0.74, 1.70)	14	0.89 (0.49, 1.50)	16	1.48 (0.85, 2.41)

[a]Diagnoses were coded according to the ICD revision in force at time of diagnosis.
[b]Males only.

TABLE 5. Distribution of Persons (%) and OR with 95% CI of Smoking by Duration of Exposure, Year of First Employment, and Exposure Probability in a Reinforced Plastics Company Among 7,368 Respondents from the 2013 Worker Survey

		Smoking Status			
	n	Never-smoker %	Ever Smoker %	Unknown %	OR (95% CI)
Duration of employment (years)					
<1	1,763	28	70	2	1.00
1–4	2,672	30	68	2	0.88 (0.76, 1.00)
5–9	1,504	32	67	1	0.82 (0.71, 0.96)
≥10	1,429	36	63	1	0.68 (0.59, 0.79)
Year of first employment					
1960–1969	390	25	73	2	1.00
1970–1979	2,301	27	71	2	0.88 (0.69, 1.13)
1980–1989	2,507	33	66	1	0.68 (0.53, 0.86)
1990–1999	1,343	34	65	1	0.63 (0.49, 0.81)
2000–2007	827	35	64	1	0.60 (0.46, 0.79)
Styrene exposure probability (%)					
1–24	1,022	31	65	4	1.00
25–49	1,355	30	68	2	1.03 (0.86, 1.23)
50–74	2,504	32	67	1	0.95 (0.81, 1.11)
75–100	2,487	31	68	1	0.98 (0.83, 1.14)

site fulfilled this criterion. The SIR values for Hodgkin lymphoma increased with increasing duration of employment were increased among workers first employed in the 1960s, and increased with increasing exposure probability, except among workers with 50%–74% exposure probability. The same pattern was evident for myeloid leukemia, except for no increased risk with early year of first employment.

The previous report of this cohort presented a slightly increased risk of leukemia among workers first employed during the early years but no increased risk of Hodgkin lymphoma, as we currently observed.[20] In a multinational European cohort study, which also included a minor part of this cohort, the SMR for neoplasm of the lymphatic and hematopoietic tissue increased with time since first exposure but with no obvious relationship to cumulative exposure, and the same pattern was evident for Hodgkin lymphoma and leukemia.[21] Other cohort studies of the reinforced industry did not observe increased risks for Hodgkin lymphoma or myeloid leukemia.[16–18] In the styrene manufacturing or the styrene-butadiene rubber industries, no associations between styrene and Hodgkin lymphoma have been observed.[9,30–32] Graff et al.[31] observed increasing risk of chronic myeloid leukemia by increasing cumulative styrene exposure; however, when adjusting for other agents in the industry (butadiene and dimethyldithiocarbamate), the association disappeared. We were not able to separate chronic from acute myeloid leukemia. Myeloid leukemia is associated with tobacco smoking[33] that may have confounded our findings; however, confounding from benzene, another documented cause of acute myeloid leukemia, is not relevant because benzene exposure is not present in the reinforced plastics industry. When interpreting our findings and those of others for the lymphohematopoietic malignancies, one must be aware of the change in diagnostic classification over time, as well as inaccuracy in diagnoses obtained for these diseases from death certificates.[2]

Elevated risk of lung cancer has also been reported in other studies of the reinforced plastics industry. Collins et al.[16] reported an increased standardized mortality ratio (SMR) for lung cancer, but with an inverse relation with cumulative and duration of exposure. Coggon et al.[17] found an association between high exposure and lung cancer among workers with ≥1 year of exposure. Ruder et al.[18,34] observed a higher SMR for lung cancer among workers with high exposure than among workers with low exposure. The increased incidence observed for tobacco-associated cancers other than lung cancer indicates a higher smoking prevalence in the study population than in the general population. Applying the method suggested by Axelson[27] and Axelson and Steenland[35] based on assumptions about smoking prevalence also suggested a slightly increased risk of lung cancer solely due to smoking.

The decreasing risk of lung cancer by duration of employment observed suggests that short-term workers were more likely to smoke. Findings from the survey were in line with this. However, it may be questioned if the survey reflects the real smoking patterns of the total study population because respondents were likely to include more nonsmokers solely because they had survived long enough to participate. Surveys are, furthermore, expected to underestimate smoking prevalence because of differential participation.[36,37] Participation was much lower for short-term workers and higher prevalence of smokers has been observed among short-term than among long-term workers.[38] We previously showed that indicators of an unhealthy lifestyle predicted length of employment in this industry.[39] Taken together, this indicates an increased prevalence of smokers compared with the general population, especially among the short-term workers that may, at least partly, explain the risk pattern seen for lung cancer.

We observed an increased SIR of mesothelioma among the male workers in the overall analysis, but the risk was not related to predictors of high styrene exposure. Glass filaments constitute together with unsaturated polyesther and styrene, the major components of glass fiber-reinforced plastics. Glass filaments were reviewed by IARC in 2002 and concluded not to increase the risk of cancer and are thus not expected to have confounded our results.[40] According to the Danish Plastic Industry Association, asbestos has not been used in the industry. But asbestos exposure has occurred in the shipyard industry and 60% of the 110 cases of mesothelioma we observed were in workers employed in shipyards. Hence, the observed increased SIR of mesothelioma is not considered to be related to styrene exposure.

An interesting finding was the increased risk of cancer of the nasal cavities and sinuses. Few other studies have been able to provide a risk estimate because of the rarity of the disease. In an earlier report from this study population, an increased risk was observed but findings were limited by only seven cases.[19] Many of the reinforced plastics companies were boat yards, and wood dust exposure is an obvious competing explanation to styrene; however, animal studies have shown increased nasal hyperplasia following styrene exposure.[4,41]

Strengths and Limitations

This study takes advantage of a large study population and a long follow-up, accounting for almost 1.7 million person-years at risk that enabled us to assess the risk of even rare cancers with reasonable power. We had virtually no loss to follow-up and thereby no noticeable selection bias. Finally, we benefited from incidence data rather than cancer mortality data, unlike most other studies in this field.[16–18,21,34] This limits issues related to diagnostic categorization and cancer survival, and is a strength. Information bias should not be an issue due to the highly validated Danish national registers.

We had no information on job title or job task but benefited from self-reported data from a large survey with a high response rate. This data ensured that we only included companies with relevant styrene exposure and enabled us to estimate the exposure probability within each company. We have previously shown that such estimates provided by colleague

reports were superior to employer or expert estimates.[42] This simple method is expected to have misclassified workers, because all employees in the same company were assigned the same exposure probability. This misclassification is, however, considered to be nondifferential and may thereby attenuate a true increased risk; especially for companies with a low exposure probability. Attenuation bias is, however, expected to be a smaller problem for companies with a high probability of exposure that were dominated by small companies and workshops with fewer than 50 employees at a given point in time. A high proportion of these workers would hence have been directly or indirectly involved in the production within a limited space and thus expected to be exposed to rather homogenous and high levels of styrene because of its high volatility.

We computed SIR values by indirect standardization using cancer rates from the general population because this approach provided stable estimates of expected numbers for the several rare cancers analyzed. By this method, we would expect a "healthy hire effect," but the overall cancer risk was increased compared with the general population in agreement with an opposite effect that was also suggested by an overall higher risk of tobacco-related cancers.

CONCLUSION

In this large study of workers of the Danish-reinforced plastics industry, no cancer site displayed consistently increased risk by duration of employment, early year of first employment, and styrene exposure probability. Risks of Hodgkin lymphoma, myeloid leukemia, and cancer of the nasal cavities increased with some of these proxies of styrene exposure. We observed an increased risk of lung cancer but it was not positively related to proxies of styrene exposure. We could not confirm increased risk of cancer of the esophagus, pancreas, kidney, or urinary bladder, or other lymphohematopoietic malignancies, as suggested in previous studies. Further studies are needed before firm conclusions about the human carcinogenicity of styrene can be made.

ACKNOWLEDGMENTS

The authors thank the three independent dealers of plastic raw materials; Hans Bjerg, Erik Olsen, and Peter Kjaer, for contributing with their valuable knowledge of this industry. The authors also thank Igor Burstyn, Jens Peter Bonde, and Elsebeth Lynge for their helpful comments of the manuscript. Finally, the authors thank the Danish Working Environment Research Fund for funding this study.

REFERENCES

1. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. *IARC Monogr Eval Carcinog Risks Hum*. 2002;82:1–556.
2. National Toxicology Program. Styrene. *Rep Carcinog*. 2011;12:383–391.
3. Committee to Review the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council. 2014.
4. Cruzan G, Cushman JR, Andrews LS, et al. Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. *J Appl Toxicol*. 2001;21:185–198.
5. Cruzan G, Cushman JR, Andrews LS, et al. Chronic toxicity/oncogenicity study of styrene in CD rats by inhalation exposure for 104 weeks. *Toxicol Sci*. 1998;46:266–281.
6. Conti B, Maltoni C, Perino G, Ciliberti A. Long-term carcinogenicity bioassays on styrene administered by inhalation, ingestion and injection and styrene oxide administered by ingestion in Sprague-Dawley rats, and para-methylstyrene administered by ingestion in Sprague-Dawley rats and Swiss mice. *Ann N Y Acad Sci*. 1988;534:203–234.
7. Ponomarkov V, Tomatis L. Effects of long-term oral administration of styrene to mice and rats. *Scand J Work Environ Health*. 1978;4(suppl 2):127–135.
8. Hodgson JT, Jones RD. Mortality of styrene production, polymerization and processing workers at a site in northwest England. *Scand J Work Environ Health*. 1985;11:347–352.
9. Bond GG, Bodner KM, Olsen GW, Cook RR. Mortality among workers engaged in the development or manufacture of styrene-based products–an update. *Scand J Work Environ Health*. 1992;18:145–154.
10. Matanoski G, Francis M, Correa-Villasenor A, Elliott E, Santos-Burgoa C, Schwartz L. Cancer epidemiology among styrene-butadiene rubber workers. *IARC Sci Publ*. 1993;127:363–374.
11. Kogevinas M, Sala M, Boffetta P, Kazerouni N, Kromhout H, Hoar-Zahm S. Cancer risk in the rubber industry: a review of the recent epidemiological evidence. *Occup Environ Med*. 1998;55:1–12.
12. Alder N, Fenty J, Warren F, et al. Meta-analysis of mortality and cancer incidence among workers in the synthetic rubber-producing industry. *Am J Epidemiol*. 2006;164:405–420.
13. Boffetta P, Adami HO, Cole P, Trichopoulos D, Mandel JS. Epidemiologic studies of styrene and cancer: a review of the literature. *J Occup Environ Med*. 2009;51:1275–1287.
14. Wong O. A cohort mortality study and a case-control study of workers potentially exposed to styrene in the reinforced plastics and composites industry. *Br J Ind Med*. 1990;47:753–762.
15. Kolstad HA, Lynge E, Olsen J. Cancer incidence in the Danish reinforced plastics industry. *IARC Sci Publ*. 1993;127:301–308.
16. Collins JJ, Bodner KM, Bus JS. Cancer mortality of workers exposed to styrene in the U.S. Reinforced plastics and composite industry. *Epidemiology*. 2013;24:195–203.
17. Coggon D, Ntani G, Harris EC, Palmer KT. Risk of cancer in workers exposed to styrene at eight British companies making glass-reinforced plastics. *Occup Environ Med*. 2015;72:165–170.
18. Ruder AM, Ward EM, Dong M, Okun AH, Davis-King K. Mortality patterns among workers exposed to styrene in the reinforced plastic boatbuilding industry: an update. *Am J Ind Med*. 2004;45:165–176.
19. Kolstad HA, Juel K, Olsen J, Lynge E. Exposure to styrene and chronic health effects: mortality and incidence of solid cancers in the Danish reinforced plastics industry. *Occup Environ Med*. 1995;52:320–327.
20. Kolstad HA, Lynge E, Olsen J, Breum N. Incidence of lymphohematopoietic malignancies among styrene-exposed workers of the reinforced plastics industry. *Scand J Work Environ Health*. 1994;20:272–278.
21. Kogevinas M, Ferro G, Andersen A, et al. Cancer mortality in a historical cohort study of workers exposed to styrene. *Scand J Work Environ Health*. 1994;20:251–261.
22. Hansen J, Lassen CF. The supplementary pension fund register. *Scand J Public Health*. 2011;39(7 suppl):99–102.
23. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7 suppl):22–25.
24. Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health*. 2011;39(7 Suppl):42–45.
25. Secretan B, Straif K, Baan R, et al.; WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens–Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol*. 2009;10:1033–1034.
26. Steenland K, Beaumont J, Halperin W. Methods of control for smoking in occupational cohort mortality studies. *Scand J Work Environ Health*. 1984;10:143–149.

27. Axelson O. Aspects on confounding in occupational health epidemiology. *Scand J Work Environ Health*. 1978;4:98–102.
28. Sonderskov J. Occupational styrene exposure and haematological diseases. A nested case-control study in the Danish reinforced plastics industry. PhD. Aarhus University, Aarhus, Denmark; 2003.
29. Osler M. Smoking habits in Denmark from 1953 to 1991: a comparative analysis of results from three nationwide health surveys among adult Danes in 1953–1954, 1986–1987 and 1990–1991. *Int J Epidemiol*. 1992;21:862–871.
30. Santos-Burgoa C, Matanoski GM, Zeger S, Schwartz L. Lymphohematopoietic cancer in styrene-butadiene polymerization workers. *Am J Epidemiol*. 1992;136:843–854.
31. Graff JJ, Sathiakumar N, Macaluso M, Maldonado G, Matthews R, Delzell E. Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. *J Occup Environ Med*. 2005;47:916–932.
32. Delzell E, Sathiakumar N, Graff J, et al. An updated study of mortality among North American synthetic rubber industry workers. *Res Rep Health Eff Inst*. 2006;132:1–63; discussion 65–74.
33. Brownson RC, Novotny TE, Perry MC. Cigarette smoking and adult leukemia. A meta-analysis. *Arch Intern Med*. 1993;153:469–475.
34. Ruder AM, Meyers AR, Bertke SJ. Mortality among styrene-exposed workers in the reinforced plastic boatbuilding industry. *Occup Environ Med*. 2016;73:97–102.
35. Axelson O, Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. *Am J Ind Med*. 1988;13:105–118.
36. West R, Zatonski W, Przewozniak K, Jarvis MJ. Can we trust national smoking prevalence figures? Discrepancies between biochemically assessed and self-reported smoking rates in three countries. *Cancer Epidemiol Biomarkers Prev*. 2007;16:820–822.
37. Christensen AI, Ekholm O, Gray L, Glümer C, Juel K. What is wrong with non-respondents? Alcohol-, drug- and smoking-related mortality and morbidity in a 12-year follow-up study of respondents and non-respondents in the Danish Health and Morbidity Survey. *Addiction*. 2015;110:1505–1512.
38. Metcalfe C, Davey Smith G, Sterne JA, Heslop P, Macleod J, Hart C. Frequent job change and associated health. *Soc Sci Med*. 2003;56:1–15.
39. Kolstad HA, Olsen J. Why do short term workers have high mortality? *Am J Epidemiol*. 1999;149:347–352.
40. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Man-made vitreous fibres. *IARC Monogr Eval Carcinog Risks Hum*. 2002;81:1–381.
41. Cruzan G, Cushman JR, Andrews LS, et al. Subchronic inhalation studies of styrene in CD rats and CD-1 mice. *Fundam Appl Toxicol*. 1997;35:152–165.
42. Kolstad HA, Sønderskov J, Burstyn I. Company-level, semi-quantitative assessment of occupational styrene exposure when individual data are not available. *Ann Occup Hyg*. 2005;49:155–165.

Styrene Exposure and Risk of Lymphohematopoietic Malignancies in 73,036 Reinforced Plastics Workers

Mette Skovgaard Christensen,[a,b] *Jesper Medom Vestergaard,*[a] *Francesco d'Amore,*[c] *Jette Sønderskov Gørløv,*[d] *Gunnar Toft,*[a,e] *Cecilia Høst Ramlau-Hansen,*[f] *Zara Ann Stokholm,*[a] *Inge Brosbøl Iversen,*[a] *Mette Schou Nissen,*[a] *Henrik Albert Kolstad*[a]

Background: Styrene is an important industrial chemical that the general population is exposed to at low levels. Previous research has suggested increased occurrence of leukemia and lymphoma among reinforced plastics workers exposed at high levels of styrene.

Methods: We followed 73,036 workers of 456 small- and medium-sized Danish reinforced plastics companies from 1968 to 2011 and investigated the exposure-response relation between cumulative styrene exposure and incidence of lymphohematopoietic malignancies. We modeled styrene exposure from employment history, survey data, and historical styrene exposure measurements. We retrieved information on lymphohematopoietic malignancies from national cancer and patient registers.

Results: We identified 665 cases overall of 21 different lymphohematopoietic malignancies or combinations thereof, each with at least 20 cases, during 1,581,976 person-years of follow-up. Initial analyses suggested higher age, sex, and calendar year-adjusted incidence rate ratios (RRs) for acute myeloid leukemia, Hodgkin lymphoma, and T-cell lymphoma with higher estimates of cumulative styrene exposure. Accounting for time since exposure showed a trend by cumulative styrene exposure ($P = 0.01$) and a doubled risk (RR = 2.4; 95% CI, 1.2, 4.6) of acute myeloid leukemia following estimated high compared with estimated low cumulative exposure during the prior 15–29 years. We observed no increased risk following exposure during more recent years and less consistent risk patterns for Hodgkin lymphoma and T-cell lymphoma.

Conclusions: This study, to our knowledge the largest epidemiologic study to date of occupational styrene exposure, suggests increased risk of acute myeloid leukemia following high styrene exposure with a latency period of about 15 years.

Keywords: Acute myeloid leukemia; Cohort study; Epidemiology; Hematological neoplasms; Hodgkin disease; Non-Hodgkin lymphoma; Occupational exposures; Styrene.

(*Epidemiology* 2018;29: 342–351)

Styrene is an important industrial chemical used in the manufacture of house wares, insulation products, tires, and a wide variety of other plastic and synthetic rubber products.[1] The general population is exposed to low levels of styrene while occupationally exposed workers may encounter much higher levels.[2] In the late 1970s, observations among workers in the synthetic rubber industry suggested styrene exposure to be related to leukemia and lymphoma occurrence.[3,4] Later studies of this industry have shown increasing risk of leukemia and non-Hodgkin lymphoma with increasing cumulative styrene exposure.[5–7] Interpretation of these results is, however, hampered by a high correlation between styrene and butadiene exposures, the latter a well-documented human carcinogen.[8]

In the reinforced plastics industry, styrene exposure levels occur that are higher than in the synthetic rubber industry, and co-exposure to other suspected carcinogens is limited.[8] A European multinational study of this industry showed increased risk of lymphoma and leukemia with increasing average exposure and time since first exposure.[9] A Danish study of a cohort that partly overlapped the European study population showed increased risk of leukemia among workers first employed in the 1960s, the period with the highest styrene exposure levels.[10] Neither the European nor the Danish study indicated increasing risk of leukemia with increasing cumulative exposure or duration of exposure.[9,10] Other studies of the reinforced plastics industry indicated no association between styrene exposure and lymphohematopoietic malignancies, and so far only major subtypes of lymphohematopoietic malignancies have been studied.[11–17]

Styrene is classified as possibly carcinogenic to humans by the International Agency for Research on Cancer based on limited human and experimental evidence.[18] Styrene was

Submitted July 13, 2017; accepted March 5, 2018.

From the [a]Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark; [b]Centre for Integrated Register-based Research, CIRRAU, Aarhus University, Aarhus, Denmark; [c]Department of Hematology, Arhus University Hospital, Aarhus, Denmark; [d]Department of Hematology, Rigshospitalet, Copenhagen, Denmark; [e]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; and [f]Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark.

For access to data, contact the Department of Occupational Medicine at Aarhus University Hospital. The analytical code used for the analyses contained herein is presented in Supplemental Digital Content, eAppendix 1.

Supportted by the Danish Working Environment Research Fund (grant number 32-2011-09).

Disclosure: The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

Correspondence: Henrik A. Kolstad, Department of Occupational Medicine, Danish Ramazzi Centre, Aarhus University Hospital, Palle Juul-Jensen Boulevard 99, DK- 8200 Aarhus C, Denmark. E-mail: henkol@rm.dk.

ISSN: 1044-3983/18/2903-0342
DOI: 10.1097/EDE.0000000000000819

listed in the National Toxicology Program Twelfth Report on Carcinogens as reasonably anticipated to be a human carcinogen based on increased mortality or incidence of cancer of the lymphohematopoietic system and the formation of DNA adducts and genetic damage in exposed workers.[8] In 2014, the assessment was reviewed by the U.S. National Research Council, the listing was maintained, and styrene is included in the National Toxicology Program Fourteenth Report on Carcinogens.[19,20]

We recently updated our previous investigations of the Danish reinforced plastics industry and observed indications of higher incidence of myeloid leukemia and Hodgkin lymphoma with longer duration of employment, earlier year of first employment in the industry, or higher styrene exposure probability when compared with the general population.[10,21–23] This study adds to these analyses by investigating the association between quantitative measures of styrene exposure and the incidence of multiple lymphohematopoietic malignancies.

METHODS

Population

The study population included employees from 456 Danish companies that ever produced reinforced plastic products from unsaturated polyester resins since the early 1960s. The cohort was originally established in the 1990s and updated in 2012.[10,21–23] We identified all 77,491 workers employed in these companies in a national pension register at any time between 1964 (the year the register was established) and 2007 and regardless of duration of employment. We excluded 56 workers diagnosed with a lymphohematopoietic malignancy and 878 who died, emigrated, or disappeared prior to start of follow-up as defined later. We also excluded 3496 workers who according to the pension register were employed in a study company in 1964 (wash-out period) and not during later years to include only participants with complete exposure histories, as well as 25 workers for whom we could not identify a vital status. The study population then comprised 73,036 workers.

The Nationwide Individual Survey, Population, and Housing Census provided information on occupation in 1970 and the Integrated Database for Labor Market Research at Statistics Denmark for 1981 and onward.[24] Occupation was coded according to Danish versions of the International Standard Classification of Occupations (ISCO) versions 1968 and 1988, respectively. The recorded occupation did not necessarily correspond with the occupation held within a study company, and only limited information was available for specific occupations related to styrene exposure. We therefore defined white collar workers (ISCO codes 1000-5999), skilled blue collar workers (ISCO codes 6000-7999), and unskilled blue collar workers (ISCO codes 8000-9999). We classified students or workers retired or receiving social benefits as "other employment" and accounted for changes in occupation over time. When information was missing for a year and could not be extrapolated from the previous year, this was classified as "unknown." Information on sex, date of birth, death, emigration, or disappearance was provided by the Danish Civil Registration System established on April 1, 1968.[25]

Lymphohematopoietic Malignancies

We identified all lymphohematopoietic malignancies registered in the Danish Cancer Registry (1943–2011) that classified malignancies according to the seventh (ICD-7, 1943–1977) and 10th (ICD-10, 1978–2011) revisions of the International Classification of Diseases and the International Classification of Diseases for Oncology, third edition (ICD-O-3, 1978–2011).[26] We defined lymphoid malignancies from the ICD-O-3 morphology codes when available, else by the ICD-10 or ICD-7 codes. Myeloid malignancies were defined only by ICD-10 or ICD-7 codes (eTable 1; http://links.lww.com/EDE/B330). Myelodysplastic syndrome, polycythemia vera, and essential thrombocythemia were not systematically recorded in the cancer register during early years and were also identified in the National Patient Register (1977–2011) that classified all hospitalizations by the eighth revision of the International Classification of Diseases (ICD-8, 1977–1993) and ICD-10 (1994–2011).[27]

Styrene Exposure Assessment

The exposure assessment included three parts: (1) estimation of styrene exposure intensity among styrene exposed workers; (2) estimation of styrene exposure probability within the study population; and (3) estimation of cumulative styrene exposure score, the principal summary styrene exposure metric. We also estimated the three components thereof: duration of employment during styrene production, mean styrene exposure intensity, and mean styrene exposure probability.

Styrene Exposure Intensity

We identified 1122 personal measurements of work room styrene concentration with a sampling time of at least 1 hour from styrene exposed workers of 133 reinforced plastics companies 1970–2011. A detailed description of an earlier version of these data is reported elsewhere.[28]

During the early 1990s, respirators were increasingly introduced in the Danish reinforced plastics industry. We therefore applied a correction factor of 0.2 for all measurements obtained ≥ 1990. The factor was based on post-shift urinary mandelic acid (the main styrene metabolite) concentrations measured in the 1990s among styrene exposed workers from this population[29] that was roughly 20% of the intensity estimated from the similarly recorded work-room air concentrations.

We modeled styrene exposure intensity by mixed-effects linear regression that included the $\log_e$-transformed styrene concentration as the dependent variable and company characteristics (main production process, main product, and decade) as the independent variables (fixed effects) and company (random effect). In the prediction, best linear unbiased estimates

of the random effects were used to account for differences between companies. We tested assumptions of normality by residual plots. We did not have access to any measurements for the earliest decade (1960s) and used a linear regression model based on styrene intensity levels for each scenario in the subsequent decades to predict the intensity levels for the scenarios in the 1960s.

Styrene Exposure Probability

We estimated styrene exposure probability within the study population based on a survey conducted between 2013 and 2014. We randomly selected a sample of present and former workers from each company stratified by decade (1964–1969, 1970–1979, 1980–1989, 1990–1999, 2000–2007) and gender. From companies with 1–99, 100–499, and ≥ 500 employees within these strata, we applied sampling fractions of 55%, 25%, and 10%. A total of 23,808 workers were selected. We excluded workers deceased, emigrated, or living in Greenland (n = 5832), workers who declined to be contacted (n = 2433), and those above 79 years of age (n = 436). A total of 15,107 workers were invited, and 11,492 responded by filling in a questionnaire (76%). The final sample was augmented by 209 participants from a similar small survey conducted in 2000 in some of the companies. Of the 11,701 respondents, 11,264 reported work tasks and 4,996 (44%) confirmed tasks consistent with styrene exposure during 1 or more decades since the 1960s.

We generated separate records for each participant's company–decade combinations (n = 20,404) that we linked with information on product and process provided for all companies by the employers or dealers of plastic raw materials and occupation and employment history as recorded in the registers. We estimated the probability of styrene exposure from these data in a mixed-effects logistic regression model that included styrene exposure (yes, no) as the dependent variable and calendar year (decades), main production process (lamination, other production processes), main product (boats, wind turbine wings, other products), gender, occupation (white-collar worker, skilled blue-collar worker, unskilled blue-collar worker, other employment, unknown), and company size (0–9, 10–49, 50–99, ≥ 100 employees) as independent variables (fixed effects). These factors were a priori expected to affect exposure probability.[30] Company was included as a random effect.

Summary Styrene Exposure Metrics

Duration of employment during years of styrene production was the number of years a participant had been employed in any of the study companies between the start and the end of styrene production in the respective companies. A styrene exposure score was obtained for each of these years by multiplying the predicted styrene exposure intensity and the predicted styrene exposure probability for the different exposure scenarios. A cumulative styrene exposure score (mg/m^3-years) was computed by adding these annual exposure scores from first to last year of employment during styrene production.

We also computed mean styrene exposure intensity by adding the predicted annual styrene exposure intensities dived by duration of employment from first to last year of styrene production. We followed the same procedure for the computation of mean exposure probability.

The Danish Data Protection Agency approved the study (j.no: 1-16-02-01-07). In Denmark, register studies and individual surveys, where biologic materials are not included, do not need approval from the Committee System on Biomedical Research Ethics. Participants in the survey were informed of the possibility to withdraw their consent of participation at any point in time. In accordance with the data confidentiality policy of Statistics Denmark, no less than four cases per cell were reported or should be inferred.

Statistical Analysis

We started follow-up at the earliest by April 1, 1968 or January 1 the year following the year of first employment during styrene production, whichever was latest. This was because we had no information on month or day of employment. For the same reason, all independent variables were lagged by 1 year. We followed workers until the date of first diagnosis of a lymphohematopoietic malignancy, death, emigration, or end of follow-up on December 31, 2011, whichever was earliest and treated all variables as time dependent.

We assessed the relation between measures of styrene exposure and lymphohematopoietic malignancies with a discrete time hazard model with person–years as the unit of analysis, yielding incidence rate ratios (RRs).[31] Styrene exposure metrics were categorized into tertiles or halves with cut-points based upon the person-year exposure distributions. Duration of employment during styrene production was categorized into 1, 2–4, and ≥ 5 years.

We analyzed all separate or grouped lymphohematopoietic malignancies with ≥ 20 cases by cumulative styrene exposure scores accrued during the full work history in the reinforced plastics industry. For malignancies indicating positive associations, we analyzed the separate exposure metrics making up the cumulative styrene exposure score: mean styrene exposure intensity, mean styrene exposure probability, and duration of employment during styrene production. We also analyzed the temporal variation with cumulative styrene exposure score within the previous < 15, 15–29, and ≥ 30 years (time window analyses). The study spanned 48 years, and the 15-year time window boundaries were defined a priori to obtain three windows of comparable width. We did not examine other windows for these analyses. We treated exposures within each window in separate models and classified styrene exposure outside the window as zero and dichotomized exposure level within the window by the median.[32]

We also fit discrete time hazard models to obtain restricted cubic spline curves of the relation between time

TABLE 1. Company Characteristics and Styrene Exposure Intensity in 133 Danish Reinforced Plastics Companies, 1970–2011

Company Characteristics	Regression Coefficient[a] (95% CI)
Intercept[b]	1.4 (0.4–2.5)
Main product	
Boats	0.6 (0.3–1.0)
Wind turbine rotor blades	0.3 (-0.1, 0.6)
Main production process	
Lamination	0.6 (0.3, 1.0)
Calendar year	
1970–1979	2.8 (1.7, 3.8)
1980–1989	2.2 (1.2, 3.3)
1990–1999	1.3 (0.0, 2.6)

[a]Regression coefficient of $\log_e$-transformed styrene exposure intensity (mg/m^3) estimated in a mixed linear regression model of 1122 personal styrene measurements obtained from 133 companies of the Danish reinforced plastics industry 1970–2011.
[b]Intercept defined by other products, other production process, and 2000–2011.

TABLE 2. Odds Ratios of Styrene Exposure by Company and Worker Characteristics in the Danish Reinforced Plastics Industry, 1964–2007

Worker and Company Characteristics	Odds Ratio[a] (95% CI)
Gender	
Female	0.2 (0.2, 0.3)
Occupation[b]	
Skilled blue collar workers	2.4 (2.2, 2. 7)
Unskilled blue collar workers	4.4 (3.9, 4.9)
Other employment	1.3 (1.1, 1.6)
Unknown	2.9 (2.5, 3.5)
Calendar year	
1970–1979	1.7 (1.3, 2.1)
1980–1989	1.9 (1.5, 2.5)
1990–1999	1.8 (1.4, 2.4)
2000–2007	1.8 (1.3, 2.4)
Main product	
Wind turbine rotor blades	2.0 (0.9, 4.8)
Other products	0.7 (0.5, 0.9)
Main production process	
Other production processes	1.1 (0.7, 1.5)
Company size[c]	
10–49	0.4 (0.3, 0.5)
50–99	0.1 (0.1, 0.2)
≥ 100	0.1 (0.1, 0.2)

Intercept = 1.5 (95% CI, 1.1, 2.2) defined as male, white collar worker, 1964–1969, boats, lamination, and < 10 employees.
[a]Odds ratio of styrene exposure estimated in a mixed-effects logistic regression model of 20,404 company-decade combinations of 11,264 workers of the Danish reinforced plastics industry, 1964–2007.
[b]Defined by the Danish version of the ISCO.
[c]Mean number of employees at a given point in time.

window exposure and lymphohematopoietic malignancies. Spline knots were set to the quintiles of the person-year distribution of styrene exposure above zero (i.e., all exposure within the exposure time windows).

We had no exposure information 2008–2011 and therefore did a sensitivity analysis by ending follow up in 2008.

Adjusted analyses included age (< 40, 40–49, 50–59, 60–69, ≥ 70 years), gender, and calendar year (< 2000, ≥ 2000) as covariates unless otherwise specified. We performed tests for linear trend by including a continuous variable of consecutive integers for the different exposure metrics. We assessed goodness of fit with Akaike's information criterion. All analyses were performed with Stata version 13 (StataCorp LP, College Station, TX).

RESULTS

The cohort accumulated 1,581,976 person-years and 665 incident cases of 21 different lymphohematopoietic malignancies with ≥ 20 cases during follow-up (eTable 1; http://links.lww.com/EDE/B330). There were 183 cases of myeloid, 476 cases of lymphoid (386 classified as B-cell and 22 as T-cell derived), and six cases of unspecified cell lineage.

Styrene exposure intensity was highest for companies producing boats, companies with lamination as the main production process, and during early years (Table 1). The probability of being exposed to styrene was highest for men, unskilled blue collar workers, workers employed in companies producing wind turbine rotor blades, and workers employed in small companies while main production process showed little impact on exposure probability (Table 2).

Table 3 shows results for the 21 lymphohematopoietic malignancies or combinations thereof with 20 or more cases by cumulative styrene exposure score accrued during the full work history and suggests increased risks for acute myeloid leukemia, Hodgkin lymphoma, and T-cell lymphoma. Increased risk was also indicated for all T-cell–derived lymphoid malignancies, but most cases were T-cell lymphoma. Lower risks were seen for myelodysplastic syndrome, other or nonspecific lymphoma, all lymphoid leukemias, all chronic lymphoid leukemias, and chronic B-cell lymphoid leukemia with higher cumulative styrene exposure score.

Table 4 presents results for acute myeloid leukemia, Hodgkin lymphoma, and T-cell lymphoma by several styrene exposure metrics accrued during the full work history and cumulative styrene exposure score accrued during the prior < 15 years, 15–29 years, and ≥ 30 years. Analyses of full work history exposure showed age, sex, and calendar year–adjusted RRs of 1.4 (95% CI, 0.7, 2.8) for acute myeloid leukemia, 1.6 (95% CI, 0.8, 2.2) for Hodgkin lymphoma, and 3.2 (95% CI, 0.9, 11.8) for T-cell lymphoma in the highest compared with the lowest cumulative exposure tertile and higher risk with longer duration of employment. The adjusted RRs of acute myeloid leukemia and T-cell lymphoma were also higher with

TABLE 3. Incidence Rate Ratios of Lymphohematopoietic Malignancies by Cumulative Styrene Exposure Score Accrued During the Complete Work History in 73,036 Workers of the Danish Reinforced Plastics Industry, 1968–2011

	Cumulative Styrene Exposure Score[a]							
	1–17 mg/m³-years (Reference)	18–70 mg/m³-years			≥ 71 mg/m³-years			
Malignancy	No. of cases[b]	No. of cases[b]	Crude RR	Adjusted RR[c] (95% CI)	No. of cases[b]	Crude RR	Adjusted RR[c] (95% CI)	P_{trend}[d]
All lymphohematopoietic malignancies	182	220	1.2	0.9 (0.8, 1.1)	263	1.4	0.9 (0.8, 1.1)	0.42
All myeloid malignancies	48	57	1.2	0.9 (0.6, 1.3)	78	1.6	0.9 (0.7, 1.4)	0.86
All myeloid leukemias	22	22	1.0	0.8 (0.4, 1.4)	40	1.8	1.1 (0.6, 2.0)	0.83
Acute myeloid leukemia	12	12	1.0	0.8 (0.3, 1.7)	26	2.2	1.4 (0.7, 2.8)	0.28
Chronic myeloid leukemia	6	7	1.2	0.7 (0.2, 2.2)	11	1.8	0.9 (0.3, 2.6)	0.99
Myelodysplastic syndrome	10	14	1.4	0.9 (0.4, 2.0)	13	1.3	0.6 (0.3, 1.4)	0.39
Polycythemia vera	12	14	1.4	0.9 (0.4, 2.0)	18	1.5	0.9 (0.4, 2.0)	0.86
All lymphoid malignancies	133	161	1.2	0.9 (0.7, 1.2)	182	1.4	0.9 (0.7, 1.1)	0.36
Hodgkin lymphoma	16	16	1.0	1.0 (0.5, 2.1)	25	1.6	1.6 (0.8, 2.2)	0.15
All non-Hodgkin lymphoma	67	80	1.2	0.9 (0.7, 1.3)	89	1.3	0.9 (0.7, 1.3)	0.58
B-cell lymphoma	49	62	1.3	1.0 (0.7, 1.5)	63	1.3	0.9 (0.6, 1.3)	0.46
Follicular B-cell lymphoma	11	13	1.2	1.0 (0.4, 2.2)	11	1.0	0.7 (0.3, 1.8)	0.46
Diffuse B-cell lymphoma	31	44	1.4	1.1 (0.7, 1.7)	45	1.5	0.9 (0.6, 1.5)	0.72
T-cell lymphoma	n.r.	n.r.	1.3	1.1 (0.3, 5.2)	n.r.	4.3	3.2 (0.9, 11.8)	0.04
Other or nonspecific lymphomas	15	14	0.9	0.8 (0.4, 1.7)	12	0.9	0.7 (0.3, 1.4)	0.29
Multiple myeloma	19	20	1.0	0.8 (0.4, 1.5)	30	1.6	0.9 (0.5, 1.7)	0.91
All lymphoid leukemias	29	40	1.4	0.9 (0.6, 1.5)	33	1.2	0.6 (0.4, 1.0)	0.04
All chronic lymphoid leukemias	24	30	1.3	0.8 (0.5, 1.4)	27	1.1	0.6 (0.3, 1.9)	0.04
Chronic B-cell lymphoid leukemia	21	28	1.3	0.9 (0.5, 1.6)	25	1.2	0.6 (0.3, 1.1)	0.08
All B-cell–derived lymphoid malignancies	107	131	1.2	1.0 (0.8, 1.3)	148	1.4	1.0 (0.7, 1.2)	0.69
All T-cell–derived lymphoid malignancies	5	4	0.8	0.7 (0.2, 2.5)	13	0.6	1.8 (0.6, 5.2)	0.18

[a]Product of annual styrene exposure probability and styrene exposure intensity summed across all years of employment during styrene production and categorized into tertiles with cut-points based upon the person-year distribution.
[b]According to the data confidentiality policy of Statistics Denmark, no less than four cases per cell must be reported or inferred.
[c]Adjusted for age (< 40, 40–49, 50–59, 60–69, ≥ 70 years), calendar year (< 2000, ≥ 2000) and gender (gender for all outcomes but T-cell lymphoma and all T-cell–derived lymphoid malignancies).
[d]*P* is from a two-sided test for linear trend using consecutive integers for each exposure category.
n.r., not reported.

higher mean exposure probability, while only the latter malignancy suggested an association with mean exposure intensity. In the time window analyses, acute myeloid leukemia showed an adjusted linear trend ($P = 0.01$) by increasing cumulative styrene exposure score and a doubled risk (RR = 2.4; 95% CI, 1.2, 4.6) for high level (≥ 46 mg/m³-years) exposure accumulated during the prior 15–29 years. Slightly lower risks were seen for cumulative exposure received ≥ 30 years earlier, and no increased risks were seen for cumulative exposure received during the last < 15 years.

We observed doubled adjusted RRs for T-cell lymphoma following high compared with low level cumulative exposure received during the prior 15–29 years (RR = 2.0; 95% CI, 0.8, 5.5) and ≥ 30 years (RR = 2.4; 95% CI, 0.7, 8.5) and decreased risk following exposure during the prior < 15 years.

For Hodgkin lymphoma, there were indications of increased adjusted RRs for high level cumulative exposure during the prior < 15 years (RR = 1.7; 95% CI, 0.8, 3.8) and ≥ 30 years (RR = 1.7; 95% CI, 0.6, 4.7), but not following cumulative exposure during the intervening 15–29 years time window.

For acute myeloid leukemia, cumulative exposure accrued during the prior 15–29 years showed the best model fit (Akaike information criterion 1103.3), while for Hodgkin lymphoma and T-cell lymphoma, the best model fit was seen for cumulative exposure received during the whole work history.

The Figure presents the restricted cubic spline curves of the relation between time window cumulative styrene exposure score and acute myeloid leukemia, Hodgkin lymphoma, and T-cell lymphoma. In the 15–29 years and ≥ 30 years time windows, gradually increasing incidence RRs of acute myeloid leukemia are seen from about 50 mg/m³-years until about 100 mg/m³-years where after the incidence RRs level off. No increased risk is apparent in the more recent exposure time window. The risk patterns for Hodgkin lymphoma and T-cell lymphoma are unstable across exposure time windows,

with levels of cumulative styrene exposure score showing increased as well as decreased incidence RRs.

When we combined exposure during the 15–29 and ≥ 30 years time windows in a post hoc analysis, the adjusted RR for T-cell lymphoma following high level exposure increased (RR = 16.34; 95% CI, 1.74, 153.01) as well as the model fit (Akaike information criterion 465.3) as shown in eTable 2; http://links.lww.com/EDE/B330. Combining the two time windows had little impact on the risk estimates or model fit for acute myeloid leukemia and Hodgkin lymphoma.

TABLE 4. Adjusted Incidence Rate Ratios of Acute Myeloid Leukemia, Hodgkin Lymphoma, and T-cell Lymphoma by Cumulative Styrene Exposure Score, Mean Styrene Exposure Intensity, Mean Styrene Exposure Probability, and Duration of Employment During Styrene Production Accrued During Different Exposure Time Periods in 73,036 Workers of the Danish Reinforced Plastics Industry, 1968–2011

Exposure Metric by Exposure Time Period	Person-years	Acute Myeloid Leukemia		Hodgkin Lymphoma		T-cell Lymphoma	
		Cases	RR (95% CI)[a]	Cases	RR (95% CI)[a]	Cases[b]	RR (95% CI)[c]
Cumulative exposure score[d], complete work history							
1–17 mg/m^3-years	526,299	12	1	16	1	n.r.	1
18–70 mg/m^3-years	528,350	12	0.8 (0.3, 1.7)	16	1.0 (0.5, 2.1)	n.r.	1.1 (0.3, 5.1)
≥ 71 mg/m^3-years	527,327	26	1.4 (0.7, 2.8)	25	1.6 (0.8, 2.2)	n.r.	3.2 (0.9, 11.8)
P_{trend}[e]			0.28		0.15		0.04
Model fit, AIC[f]			1107.1		1280.6		469.7
Mean exposure intensity[g], complete work history							
1–11 mg/m^3	527,260	13	1	19	1	n.r.	1
12–39 mg/m^3	518,306	16	0.9 (0.4, 1.8)	22	1.2 (0.6, 2.2)	n.r.	1.9 (0.5, 7.5)
≥ 40 mg/m3	536,410	21	1.0 (0.5, 2.1)	16	0.8 (0.4, 1.6)	n.r.	2.5 (0.7, 9.5)
P_{trend}[e]			0.94		0.47		0.17
Model fit, AIC[f]			1109.7		1281.7		473.1
Mean exposure probability[h], complete work history							
1–22%	527,238	15	1	21	1	n.r.	1
23–57%	526,625	19	1.4 (0.7, 2.8)	15	0.7 (0.3, 1.3)	n.r.	1.6 (0.5, 5.0)
≥ 58%	528,113	16	1.5 (0.7, 3.1)	21	0.9 (0.5, 1.7)		2.2 (0.7, 6.7)
P_{trend}[e]			0.31		0.83		0.17
Model fit, AIC[f]			1108.6		1281.6		473.3
Duration of employment, complete work history							
< 1 year	732,439	20	1	23	1	n.r.	1
1–4 years	584,904	14	0.8 (0.4, 1.7)	20	1.1 (0.6, 2.0)	n.r.	1.2 (0.4, 3.4)
≥ 5 years	264,633	16	1.6 (0.4, 3.1)	14	1.7 (0.9, 3.3)	n.r.	1.6 (0.6, 4.8)
P_{trend}[e]			0.23		0.17		0.40
Model fit, AIC[f]			1106.7		1280.9		474.5
Cumulative exposure score[d], < 15 years prior							
0 mg/m^3-years	636,402	28	1	20	1	n.r.	1
1–28 mg/m^3-years	472,777	10	1.0 (0.5, 2.2)	16	1.2 (0.6, 2.5)	n.r.	0.6 (0.1, 2.3)
≥ 28 mg/m^3-years	472,797	12	0.8 (0.4, 1.7)	21	1.7 (0.8, 3.8)	n.r.	0.2 (0.0, 1.5)
P_{trend}[e]			0.60		0.17		0.09
Model fit, AIC[f]			1109.5		1281.1		471.5
Cumulative exposure score[d], 15–29 years prior							
0 mg/m^3-years	957,387	18	1	38	1	n.r.	1
1-45 mg/m^3-years	312,291	10	1.3 (0.6, 3.0)	12	1.2 (0.6, 2.3)	n.r.	0.9 (0.2, 3.3)
≥ 46 mg/m^3-years	312,298	22	2.4 (1.2, 4.6)	7	0.6 (0.3, 1.4)	n.r.	2.0 (0.8, 5.5)

(*Continued*)

TABLE 4. (*Continued*)

Exposure Metric by Exposure Time Period	Person-years	Acute Myeloid Leukemia		Hodgkin Lymphoma		T-cell Lymphoma	
		Cases	RR (95% CI)[a]	Cases	RR (95% CI)[a]	Cases[b]	RR (95% CI)[c]
P_{trend}[e]			0.01		0.36		0.17
Model fit, AIC[f]			1103.3		1281.0		472.6
Cumulative exposure score[d], ≥ 30 years prior							
0 mg/m^3-years	1,390,047	37	1	44	1	n.r.	1
1-45 mg/m^3-years	95,981	7	2.1 (0.8, 5.5)	7	2.25 (0.9, 5.9)	n.r.	2.8 (0.8, 9.6)
≥ 45 mg/m^3-years	95,948	6	1.6 (0.6, 4.3)	6	1.7 (0.6, 4.7)	n.r.	2.4 (0.7, 8.5)
P_{trend}[e]			0.28		0.21		0.15
Model fit, AIC[f]			1107.5		1280.3		472.1

[a]Adjusted for age (< 40, 40-49, 50-59, 60-69, ≥ 70 years), calendar year (< 2000, ≥ 2000) and gender.
[b]According to the data confidentiality policy of Statistics Denmark, no less than four cases per cell must be reported or inferred.
[c]Adjusted for age (< 40, 40-49, 50–59, 60–69, ≥ 70 years) and calendar year (< 2000, ≥ 2000).
[d]Product of annual styrene exposure intensity and styrene exposure probability summed across all years of employment during styrene production and dichotomized by the median of the person-year distributions above zero.
[e]*P* is from a two-sided test for linear trend using consecutive integers for each exposure category.
[f]AIC, Akaike's information criterion.
[g]Styrene exposure intensity averaged across all years of employment during styrene production and dichotomized by the median of the person-year distributions above zero.
[h]Styrene exposure probability averaged across all years of employment during styrene production and dichotomized by the median of the person-year distributions above zero.
n.r., not reported.

Analyses ending follow up in 2008 included 43 cases of acute myeloid leukemia, 49 cases of Hodgkin lymphoma, and 16 cases of T-cell lymphoma and showed results quite similar to those presented in Table 4 (eTable 3; http://links.lww.com/EDE/B330).

DISCUSSION

In this large, long-term follow-up study of workers exposed to styrene in the reinforced plastics industry, we observed higher incidence RRs for acute myeloid leukemia with higher cumulative styrene exposure scores received during the prior ≥ 15 years. No increased risks were seen following cumulative exposure received during the prior < 15 years. There were less consistent indications of increased risks of Hodgkin lymphoma and T-cell lymphoma following cumulative exposure.

Among styrene-exposed reinforced plastics workers, Collins et al.[16] observed eight deaths from acute myeloid leukemia in the highest category of cumulative exposure corresponding to a standardized mortality ratio (SMR) of 1.27 (95% CI, 0.55–2.50). No increased acute myeloid leukemia mortality was seen for all workers (SMR = 0.85; 95% CI, 0.47–1.43). A previous European study of a cohort, that partly overlapped an earlier version of the current study population, showed no increased mortality for unspecified myeloid leukemia based on 16 cases (SMR = 1.10; 95% CI, 0.63, 1.79).[9] We recently suggested a 50% increased incidence of unspecified myeloid leukemia for long-term workers (standardized incidence rate ratio [SIR] = 1.56; 95% CI, 0.98–2.36), but no increased incidence (SIR = 1.06; 95% CI, 0.86, 1.28) for all workers of the current population when compared with the general Danish population.[23] Other studies of the reinforced plastics industry have not analyzed acute myeloid leukemia or other myeloid leukemias.[12–17]

The risk of T-cell lymphoma has not previously been studied following styrene exposure in the reinforced plastics industry. We observed an SIR value of 1.12 (95% CI, 0.81, 1.51) for unspecified non-Hodgkin lymphoma among long-term workers of the present population and an SIR of 0.97 (95% CI, 0.86, 1.10) for all workers, but T-cell lymphoma comprised only 8% of all non-Hodgkin lymphomas.[23] Other studies of the reinforced plastics industry have not suggested increased risk of non-Hodgkin lymphoma with higher cumulative styrene exposure, but one study combining Hodgkin and non-Hodgkin lymphomas suggested higher mortality with higher average exposure.[9,16,33]

We observed SIR values for Hodgkin lymphoma of 1.98 (95% CI, 0.99, 3.54) and 1.21 (95% CI, 0.93, 1.54) in long-term workers and all workers of the current population.[23] Other studies of the reinforced plastics industry have shown no increased mortality.[9,16,33]

A study within the synthetic rubber industry suggested an increased risk ratio (adjusted for butadiene exposure) of acute myeloid leukemia for high (about > 30 mg/m^3-years) compared with low cumulative styrene exposure based on 26 cases. However, no increased mortality was seen in external analyses based on a subset of 13 cases.[6,34] Only a few cases of Hodgkin lymphoma were observed in this industry; these cases did not exceed the expected numbers calculated from national rates.[7,34] Indications of a positive association with styrene exposure were observed for non-Hodgkin lymphoma, but results for subtypes were not presented.[6,7,34] A population-based case–control study showed no association between T-cell lymphoma and styrene exposure.[35]

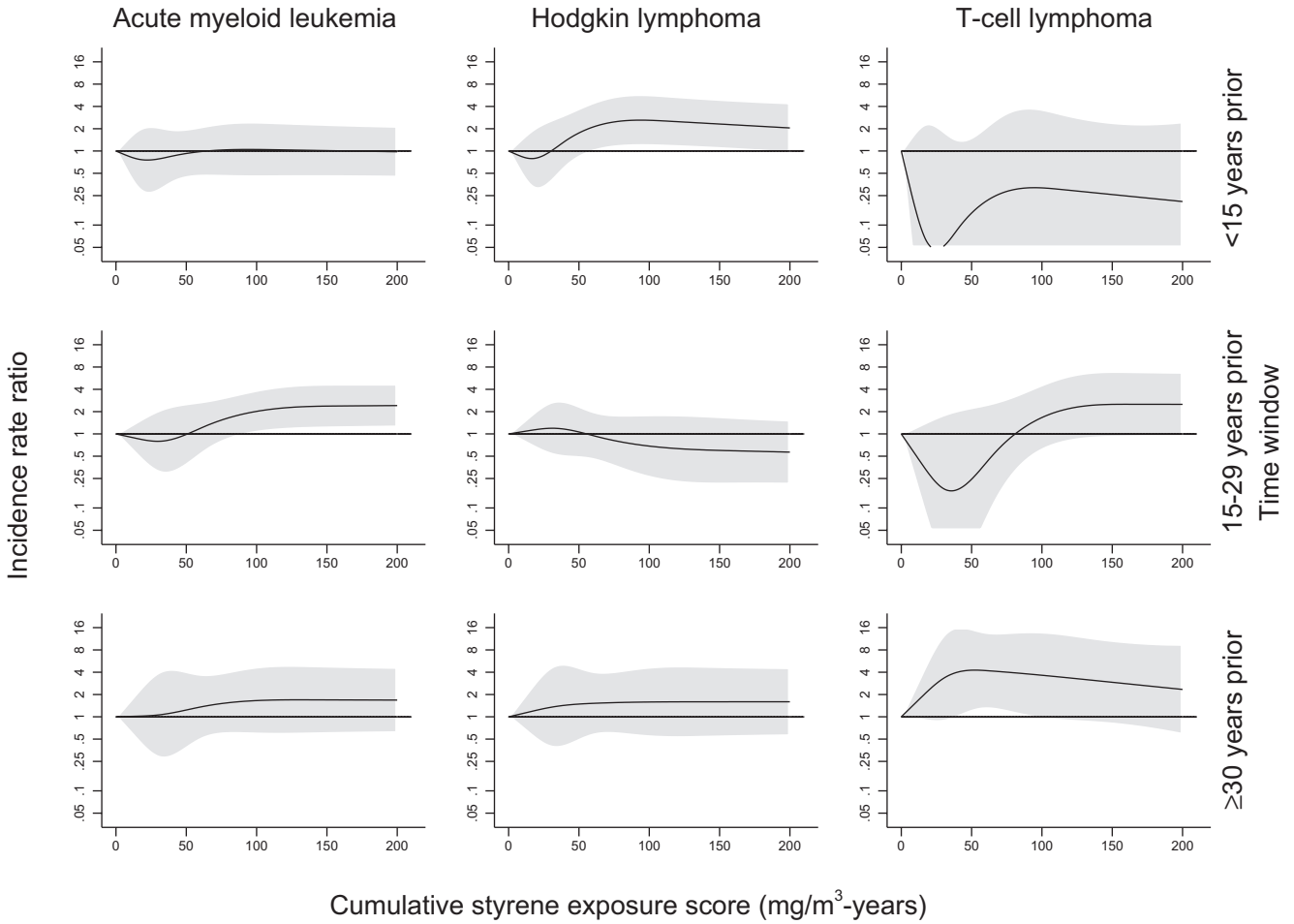


FIGURE. Restricted cubic spline fits of adjusted incidence RRs of acute myeloid leukemia, Hodgkin lymphoma, and T-cell lymphoma by cumulative styrene exposure score accrued during different time periods in 73,036 workers of the Danish reinforced plastics industry, 1968–2011.

Lymphohematopoietic malignancies comprise several different biologic and clinical subtypes with documented and expected different risk factors.[36,37] The detailed and comprehensive national Danish registers made us able to scrutinize the occurrence of many of these rare diseases among the few high level styrene exposed workers of the reinforced plastics industry as rarely done in an industry cohort like the current. The small number of cases was a limitation but also a strength because the rarity of the diseases according to a deterministic approach to causation indicates few causes and thus the potential for strong effect estimates.[38–40]

Our principal exposure metric was a combination of styrene exposure intensity, styrene exposure probability, and duration of employment during styrene production that does not allow quantitative risk assessment but quantitative evaluation of exposure response relations. Each component of the metric was estimated with considerable uncertainty, except perhaps duration of employment since employment records were expected to be complete and accurate. This may explain why this metric was the most consistent predictor of acute myeloid leukemia, Hodgkin lymphoma, and T-cell lymphoma risk. Imprecision in exposure estimates will reduce study power and increase the risk of overlooking truly increased risks and is in most cases expected to attenuate exposure-response relations. On the other hand, due to grouping of exposure measures, we would expect predominance of Berkson type error that is expected to yield unbiased risk estimates.[41]

Because we relied on registers with a high coverage, the public health care system in Denmark has no user payment, and we used no self-reported information when classifying the individual workers, selection bias, and information bias should not have major impact on our results.

We were only able to adjust analyses for age, gender, and calendar year. Benzene, tobacco smoke, ionizing radiation, and chemotherapy are established risk factors for acute myeloid leukemia and could have confounded our results, but neither benzene, ionizing radiation, nor other suspected carcinogens such as butadiene are present in the reinforced plastics industry.[42–44] We recently observed declining smoking prevalence by increasing duration of employment and thus

cumulative styrene exposure in this population, and this does not indicate that our results are inflated by smoking.[23]

We screened the risk of 21 lymphohematopoietic malignancies or combinations thereof following styrene exposure, and our results for acute myeloid leukemia may be a chance finding.

Styrene is metabolized to styrene-7,8-oxide that has shown genotoxic effects through formation of DNA adducts and single-strand breaks in human lymphocytes in a dose-related manner.[2] Chromosome aberrations in hematopoietic stem cells and progenitor cells may develop into acute myeloid leukemia; we previously observed acute myeloid leukemia with clonal chromosomal aberrations to be associated with earlier styrene exposure and genotoxicity is a possible explanation of our findings for acute myeloid leukemia.[45–47]

In conclusion, this epidemiologic study of reinforced plastics industry workers, to our knowledge the largest to date, suggests increased risk of acute myeloid leukemia following high-level styrene exposure with a latency period of about 15 years, a finding that finds some support from studies in the synthetic rubber industry. However, little is known about the risk of acute myeloid leukemia following styrene exposure. Pooling existing styrene exposed industrial cohorts enabling analyses of acute myeloid leukemia and other biologic and clinical subtypes of lymphohematopoietic malignancies should corroborate or refute the current findings.

ACKNOWLEDGMENTS

The authors thank Hans Bjerg, Erik Olsen, and Peter Kjaer for contributing with their valuable knowledge of this industry. The authors also thank Igor Burstyn, Jens Peter Bonde, and Elsebeth Lynge for their helpful comments on earlier versions of the article.

REFERENCES

1. Cohen JT, Carlson G, Charnley G, et al. A comprehensive evaluation of the potential health risks associated with occupational and environmental exposure to styrene. *J Toxicol Environ Health B Crit Rev*. 2002;5:1–265.
2. National Toxicology Program. Final report on carcinogens background document for styrene. *Rep Carcinog Backgr Doc*. 2008;(8-5978):i–462.
3. Meinhardt TJ, Young RJ, Hartle RW. Epidemiologic investigations of styrene-butadiene rubber production and reinforced plastics production. *Scand J Work Environ Health*. 1978;4 (Suppl 2):240–246.
4. Meinhardt TJ, Lemen RA, Crandall MS, Young RJ. Environmental epidemiologic investigation of the styrene-butadiene rubber industry. Mortality patterns with discussion of the hematopoietic and lymphatic malignancies. *Scand J Work Environ Health*. 1982;8:250–259.
5. Matanoski G, Elliott E, Tao X, Francis M, Correa-Villasenor A, Santos-Burgoa C. Lymphohematopoietic cancers and butadiene and styrene exposure in synthetic rubber manufacture. *Ann N Y Acad Sci*. 1997;837:157–169.
6. Graff JJ, Sathiakumar N, Macaluso M, Maldonado G, Matthews R, Delzell E. Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. *J Occup Environ Med*. 2005;47:916–932.
7. Sathiakumar N, Brill I, Leader M, Delzell E. 1,3-Butadiene, styrene and lymphohematopoietic cancer among male synthetic rubber industry workers—preliminary exposure-response analyses. *Chem Biol Interact*. 2015;241:40–49.
8. National Toxicology Program. Styrene. *Rep Carcinog*. 2011;12:383–39s1.
9. Kogevinas M, Ferro G, Andersen A, et al. Cancer mortality in a historical cohort study of workers exposed to styrene. *Scand J Work Environ Health*. 1994;20:251–261.
10. Kolstad HA, Lynge E, Olsen J, Breum N. Incidence of lymphohematopoietic malignancies among styrene-exposed workers of the reinforced plastics industry. *Scand J Work Environ Health*. 1994;20:272–278.
11. Okun AH, Beaumont JJ, Meinhardt TJ, Crandall MS. Mortality patterns among styrene-exposed boatbuilders. *Am J Ind Med*. 1985;8:193–205.
12. Wong O. A cohort mortality study and a case-control study of workers potentially exposed to styrene in the reinforced plastics and composites industry. *Br J Ind Med*. 1990;47:753–762.
13. Wong O, Trent LS, Whorton MD. An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup Environ Med*. 1994;51:386–396.
14. Coggon D, Osmond C, Pannett B, Simmonds S, Winter PD, Acheson ED. Mortality of workers exposed to styrene in the manufacture of glass-reinforced plastics. *Scand J Work Environ Health*. 1987;13:94–99.
15. Ruder AM, Ward EM, Dong M, Okun AH, Davis-King K. Mortality patterns among workers exposed to styrene in the reinforced plastic boatbuilding industry: an update. *Am J Ind Med*. 2004;45:165–176.
16. Collins JJ, Bodner KM, Bus JS. Cancer mortality of workers exposed to styrene in the U.S. Reinforced plastics and composite industry. *Epidemiology*. 2013;24:195–203.
17. Ruder AM, Meyers AR, Bertke SJ. Mortality among styrene-exposed workers in the reinforced plastic boatbuilding industry. *Occup Environ Med*. 2016;73:97–102.
18. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. *IARC Monogr Eval Carcinog Risks Hum*. 2002;82:1–556.
19. *Committee to Review the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council*. Washington, DC: National Academy of Sciences; 2014.
20. National Toxicology Program. *Report on Carcinogens, Fourteenth Edition*. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. Available at: http://ntp.niehs.nih.gov/go/roc14/. Accessed November 16, 2017.
21. Kolstad HA, Lynge E, Olsen J. Cancer incidence in the Danish reinforced plastics industry. *IARC Sci Publ*. 1993;127:301–308.
22. Kolstad HA, Juel K, Olsen J, Lynge E. Exposure to styrene and chronic health effects: mortality and incidence of solid cancers in the Danish reinforced plastics industry. *Occup Environ Med*. 1995;52:320–327.
23. Christensen MS, Hansen J, Ramlau-Hansen CH, Toft G, Kolstad H. Cancer incidence in workers exposed to styrene in the Danish-reinforced plastics industry, 1968-2012. *Epidemiology*. 2017;28:300–310.
24. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health*. 2011;39 (7 Suppl):12–16.
25. Pedersen CB. The Danish civil registration system. *Scand J Public Health*. 2011;39(7 Suppl):22–25.
26. Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health*. 2011;39(7 Suppl):42–45.
27. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 Suppl):30–33.
28. Kolstad HA, Sønderskov J, Burstyn I. Company-level, semi-quantitative assessment of occupational styrene exposure when individual data are not available. *Ann Occup Hyg*. 2005;49:155–165.
29. Kolstad HA, Bonde JP, Spano M, et al. Change in semen quality and sperm chromatin structure following occupational styrene exposure. ASCLEPIOS. *Int Arch Occup Environ Health*. 1999;72:135–141.
30. Serdar B, Tornero-Velez R, Echeverria D, Nylander-French LA, Kupper LL, Rappaport SM. Predictors of occupational exposure to styrene and styrene-7,8-oxide in the reinforced plastics industry. *Occup Environ Med*. 2006;63:707–712.
31. Richardson DB. Discrete time hazards models for occupational and environmental cohort analyses. *Occup Environ Med*. 2010;67:67–71.
32. Checkoway H, Pearce N, Hickey JL, Dement JM. Latency analysis in occupational epidemiology. *Arch Environ Health*. 1990;45:95–100.

33. Coggon D, Ntani G, Harris EC, Palmer KT. Risk of cancer in workers exposed to styrene at eight British companies making glass-reinforced plastics. *Occup Environ Med*. 2015;72:165–170.
34. Sathiakumar N, Graff J, Macaluso M, Maldonado G, Matthews R, Delzell E. An updated study of mortality among North American synthetic rubber industry workers. *Occup Environ Med*. 2005;62:822–829.
35. Cocco P, t'Mannetje A, Fadda D, et al. Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. *Occup Environ Med*. 2010;67:341–347.
36. Morton LM, Slager SL, Cerhan JR, et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr*. 2014;2014:130–144.
37. Eastmond DA, Keshava N, Sonawane B. Lymphohematopoietic cancers induced by chemicals and other agents and their implications for risk evaluation: an overview. *Mutat Res Rev Mutat Res*. 2014;761:40–64.
38. Rothman KJ. Causes. *Am J Epidemiol*. 1976;104:587–592.
39. Olsen J. What characterises a useful concept of causation in epidemiology? *J Epidemiol Community Health*. 2003;57:86–88.
40. Kolstad H, Lynge E, Olsen J, Sabroe S. Occupational causes of some rare cancers. A literature review. *Scand J Soc Med Suppl*. 1992;48:1–148.
41. Armstrong BG. Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med*. 1998;55:651–656.
42. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*. 2012;100:9–562.
43. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Tobacco Smoke and Involuntary Smoking*. Lyon, France: International Agency for Research on Cancer; 2004.
44. Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. *Lancet*. 2013;381:484–495.
45. Pedersen-Bjergaard J, Christiansen DH, Desta F, Andersen MK. Alternative genetic pathways and cooperating genetic abnormalities in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia. *Leukemia*. 2006;20:1943–1949.
46. Smith MT, Skibola CF, Allan JM, Morgan GJ. Causal models of leukaemia and lymphoma. *IARC Sci Publ*. 2004;157:373–392.
47. Kolstad HA, Pedersen B, Olsen J, et al. Clonal chromosome aberrations in myeloid leukemia after styrene exposure. *Scand J Work Environ Health*. 1996;22:58–61.

OEM Online First, published on March 14, 2018 as 10.1136/oemed-2017-104974

OPEN ACCESS

SHORT REPORT

Sinonasal adenocarcinoma following styrene exposure in the reinforced plastics industry

Mette Schou Nissen,[1] Zara Ann Stokholm,[1] Mette Skovgaard Christensen,[1] Vivi Schlünssen,[2,3] Jesper Medom Vestergaard,[1] Inge Brosbøl Iversen,[1] Henrik Albert Kolstad[1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2017-104974).

[1]Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Public Health, Danish Ramazzini Centre, Aarhus University, Aarhus, Denmark
[3]National Research Centre for the Working Environment, Copenhagen, Denmark

Correspondence to
Dr Henrik Albert Kolstad, Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus 8000, Denmark; henkol@rm.dk

Received 19 December 2017
Revised 6 February 2018
Accepted 17 February 2018

ABSTRACT

Background Sinonasal adenocarcinoma is a rare disease expected to have rare causes and potential for strong risk factors as reflected by the strong association with occupational wood dust exposure. High level styrene exposure is a rare and suspected carcinogen, and this study examines the exposure–response relation between occupational styrene exposure, sinonasal adenocarcinoma and other subtypes.

Methods We followed 73 092 styrene-exposed workers from 1968 to 2011 and identified sinonasal cancers in the Danish Cancer Registry. We modelled cumulative styrene exposure and estimated incidence rates and age, sex and wood-industry adjusted ORs.

Results During 1 585 772 person-years, we observed nine cases of adenocarcinoma, corresponding to a fivefold non-significantly increased OR for estimates of high versus low cumulative styrene exposure (OR 5.11, 95% CI 0.58 to 45.12). The increased risk was confined to exposure received during the recent 15 years. The other histological subtypes showed no increased risk.

Conclusion This study suggests increased risk of sinonasal adenocarcinoma following styrene exposure. The observations are, however, few, confounding from wood dust exposure cannot be ruled out, and additional studies are needed before firm conclusions can be drawn.

Key messages

What is already known about this subject?
- Sinonasal adenocarcinoma is a rare disease expected to have rare causes and potential for strong risk factors as reflected by the strong association with occupational wood dust exposure.

What are the new findings?
- High-level occupational styrene exposure is rare and we observed nine cases and a fivefold, non-significantly increased risk of sinonasal adenocarcinoma following high-level cumulative styrene exposure among 73 000 reinforced plastics workers.

How might this impact on policy or clinical practice in the foreseeable future?
- This finding may contribute together with other epidemiological, animal and mechanistic data to the assessment of the human carcinogenicity of styrene.

INTRODUCTION

Fifty years ago, Esme Hadfield, an alert ear-nose-and-throat clinician, observed a cluster of sinonasal adenocarcinomas among furniture makers in Buckinghamshire, UK, exposed to high levels of wood dust.[1] Later, several epidemiological studies have confirmed these observations by showing a 10-fold to 40-fold increased risk of sinonasal adenocarcinoma following wood dust exposure and today the International Agency for Research on Cancer (IARC) considers the association well established.[2 3] Sinonasal adenocarcinoma is a rare cancer and these findings add to similar observations of other rare cancers strongly associated with specific and rare occupational exposures like soot and scrotal cancer and vinyl chloride and angiosarcoma of the liver.[4 5] They all provided early and strong signals of carcinogenesis probably because rare diseases according to a deterministic approach to causality are expected to have rare causes and thus potential for large effect measures.[6]

We recently suggested an increased risk of sinonasal cancer among reinforced plastics workers exposed to styrene.[7] Styrene is classified as possibly carcinogenic to humans by IARC and was listed in the National Toxicology Programme 12th Report on Carcinogens as reasonably anticipated to be a human carcinogen.[8] High-level styrene exposure occurs almost exclusively among a small number of reinforced plastic workers.[7] We here add to our recent findings by examining the exposure–response relation between quantitative measures of cumulative occupational styrene exposure and sinonasal adenocarcinoma and other histological subtypes.

METHODS

The study population was 73 092 workers that according to a national pension register of all employees in Denmark were ever employed from 1964 to 2007 in 456 small-sized and medium-sized companies producing reinforced plastics. The register provided annual information on employment in these companies and any other company since 1964. Statistics Denmark provided information on occupation 1970–2007. In the National Danish Cancer Registry, we identified all incident cases of sinonasal cancer classified by the

Check for updates

To cite: Nissen MS, Stokholm ZA, Christensen MS, *et al*. *Occup Environ Med* Epub ahead of print: [please include Day Month Year]. doi:10.1136/oemed-2017-104974

International Classification of Diseases revision 7 (ICD-7) code 160 (1968–1977) and ICD-10 codes C30 and C31 (1978–2011). According to the morphology codes of the ICD for Oncology, third edition, we defined squamous cell carcinomas (8070/3, 8071/3), adenocarcinomas (8140/3, 8440/3, 8260/3) and other histological subtypes (8002/3, 8020/3, 8200/3, 8430/3, 8720/3, 9680/3, 9999/3).

We modelled styrene exposure intensity from 1122 personal styrene measurements and company characteristics (production process, product and decade) obtained from 133 reinforced plastics companies 1970–2011. We modelled styrene exposure probability in regression models based on survey exposure information from 11 264 present and former employees of all companies linked with information on occupation, sex, product, production process, company size and calendar year available for the complete population. For each worker and each year of employment during styrene production in any of the study companies, we computed a styrene exposure score as the product of predicted styrene exposure probability and predicted styrene exposure intensity. These scores were added across all years of employment to obtain a cumulative styrene exposure score that was categorised into low and high based on the person-year median. We refrained from categorising into tertiles (or more categories) since no case of adenocarcinoma occurred in the median category. We also estimated the three components thereof: duration of employment during styrene production, mean styrene exposure intensity and mean styrene exposure probability. Detailed information on the study population and exposure assessment is described elsewhere.[9]

The study population was followed from 1968 or from 1 January following the year of first employment during styrene production until an incident diagnosis of sinonasal cancer, death, emigration, disappearance or end of follow-up by 31 December 2011, whichever came first.

In the initial analyses, we computed the incidence rates (IR) and estimated crude incidence rate ratios (IRR) with 95% CI by cumulative styrene exposure score with a discrete survival function. To account for age, sex and wood dust exposure and due to the small number of cases, we then conducted a case–control study nested within the study population. We randomly selected 10 controls for each case by incidence density sampling, matched on age (within 2 years), sex and employment in a reinforced plastics company producing boats or employment in wood industry (sawmilling and planning of wood, manufacture of veneer boards and wood-based boards, manufacture of builders' carpentry and joinery, manufacture of wooden packaging, furniture industry, carpentry and joinery business) since 1964 (never, ever or unknown). With conditional logistic regression, we estimated adjusted OR with 95% CI by cumulative styrene exposure score and the other exposure metrics accrued during the full work history and during specified time windows (<15 years prior, 15–29 years prior and ≥30 years prior). We estimated the log-linear relation with the original continuous variables. Analyses were performed with STATA V. 13.1.

In accordance with the data confidentiality policy of Statistics Denmark, no less than four cases per cell were reported or should be inferred, and for that reason, we only present the overall number of cases from each histological subcategory.

RESULTS

During the 1 585 772 accumulated person-years, we identified 37 sinonasal cancers: nine adenocarcinomas, 15 squamous cell carcinomas, 13 other histological subtypes and 370 controls, 10 for each case.

We observed one case of adenocarcinoma per 100 000 person-years for a high cumulative styrene exposure score (≥37 mg/m^3-years, online Supplementary table 1). This corresponded to an eightfold increased crude risk (IRR 8.00, 95% CI 1.00 to 63.97). No increased risk was seen for squamous cell carcinomas or the other histological subtype category. The age, sex and wood industry matched analyses showed a fivefold increased OR of

Table 1 ORs with 95% CI of sinonasal adenocarcinoma, squamous cell carcinoma and a category of other histological subtypes by styrene exposure in the Danish reinforced plastics industry, 1968–2011*

	Adenocarcinoma (n=9)		Squamous cell carcinoma (n=15)		Other histological subtypes (n=13)	
Exposure metric	**OR† (95% CI)**	**OR‡ (95% CI)**	**OR† (95% CI)**	**OR‡ (95% CI)**	**OR† (95% CI)**	**OR‡ (95% CI)**
Cumulative styrene exposure score						
<37 mg/m^3-years	1. 00 (reference)	1.00 (reference)	1. 00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥37 mg/m^3-years	4.02 (0.44 to 36.6)	5.11 (0.58 to 45.12)	1.30 (0.37 to 4.57)	1.15 (0.34 to 3.89)	0.88 (0.28 to 2.80)	0.74 (0.22 to 2.42)
Per 100 mg/m^3-years	1.36 (1.09 to 1.68)	1.08 (0.96 to 1.21)	0.96 (0.81 to 1.14)	1.02 (0.83 to 1.25)	0.80 (0.51 to 1.20	0.75 (0.46 to 1.23)
Mean styrene exposure intensity						
<23 mg/m^3	1. 00 (reference)	1.00 (reference)	1. 00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥23 mg/m^3	1.85 (0.34 to 10.20)	2.06 (0.38 to 11.25)	0.45 (0.14 to 1.47)	0.43 (0.14 to 1.32)	0.46 (0.14 to 1.51)	0.45 (0.13 to 1.53)
Per 10 mg/m^3	1.17 (1.04 to 1.32)	1.08 (0.98 to 1.18)	0.99 (0.87 to 1.12)	0.98 (0.86 to 1.11)	0.97 (0.87 to 1.09)	0.95 (0.84 to 1.07)
Mean styrene exposure probability						
<37%	1. 00 (reference)	1.00 (reference)	1. 00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥37%	2.08 (0.49 to 8.85)	1.81 (0.39 to 8.45)	1.22 (0.41 to 3.62)	1.40 (0.47 to 4.20)	1.45 (0.46 to 4.57)	0.94 (0.29 to 3.04)
Per %	1.02 (0.99 to 1.05)	1.02 (0.99 to 1.05)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)	0.99 (0.97 to 1.01)
Duration of employment during styrene production						
<5 years	1. 00 (reference)	1.00 (reference)	1. 00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥5 years	3.72 (0.88 to 15.64)	2.50 (0.64 to 9.73)	0.67 (0.18 to 2.46)	0.96 (0.26 to 3.55)	0.33 (0.04 to 2.59)	0.24 (0.03 to 1.95)
Per year	1.07 (0.96 to 1.19)	1.07 (0.95 to 1.20)	0.97 (0.86 to 1.10)	1.04 (0.91 to 1.19)	0.95 (0.81 to 1.12)	0.95 (0.80 to 1.14)

*In accordance with the data confidentiality policy of Statistics Denmark, no less than four cases per cell were reported or should be inferred, and for that reason, only the overall number of cases are presented.
†Cases and controls are matched on age and sex.
‡Cases and controls are matched on age, sex and employment in a reinforced plastics company producing boats or in wood industry (never, ever, unknown).

adenocarcinoma for a high cumulative styrene exposure score (OR 5.11; 95% CI 0.58 to 45.12, table 1). High mean styrene exposure intensity, high styrene exposure probability and long duration of employment during styrene production all showed approximately doubled risks of sinonasal adenocarcinoma. For adenocarcinoma, positive log-linear relations were seen for all styrene exposure metrics; however, none were of statistical significance. We observed a fourfold increased risk of adenocarcinoma following exposure received during the recent <15 years (OR 3.88; 95% CI 0.71 to 21.05) and a decreased risk following more distant exposure (online Supplementary table 2). No increased risks were indicated for squamous cell carcinomas or the other histological subtype category.

DISCUSSION

We observed a fivefold non-significantly increased risk of sinonasal adenocarcinoma following a high level cumulative styrene exposure score. The increased risk was confined to exposure received during the recent 15 years. No increased risks were apparent for other histological subtypes.

To our knowledge, no other epidemiological study has evaluated the risk of sinonasal cancer following styrene exposure. Results for exposure to unspecified organic solvents, which may include styrene, have been inconsistent. Animal studies have shown increased occurrence of lung tumours in mice exposed to styrene.[10] Styrene is metabolised to styrene-7,8-oxide, which has genotoxic effects through formation of DNA adducts and single-strand breaks and this could indicate mutagen-initiated carcinogenesis.[8] A cytotoxic effect of styrene has also been suggested, and regenerative hyperplasia has been shown in respiratory tissues.[10] The exclusive association with recent styrene exposure is more suggestive of a promoter than an initiator effect and differs from that seen for wood dust showing a latency period of about 20 years.[2] The exclusive association seen for adenocarcinomas suggests this histological subtype to be more susceptible to environmental exposures.

Information on outcome and exposure relied on sources independent of the participants and misclassification of exposure and outcome are expected to be non-differential and unlikely to explain our findings. Furthermore, our grouping of exposure should mainly lead to Berkson type error causing little or no bias of the exposure response relation. Due to high coverage of the registries, a public healthcare system in Denmark with no user payment, recruitment and follow-up were almost complete.

Four of the nine cases of andenocarcinoma were employed in a reinforced plastics company producing boats and potentially wood dust exposed, for example, during manufacturing of interior fitting or employed in other wood industry at some point in time since 1964. Matching controls on this information should have reduced confounding from such exposure even if this took place more than 20 years earlier since the first case of adenocarcinoma occurred in the 1990s. But residual confounding cannot be ruled out due to the limited information on wood dust exposure, for example, related to production of wooden moulds within the industry.

Nickel, leather dust and formaldehyde are other documented or suspected risk factors for sinonasal cancer but they are not expected to be present in the reinforced plastics industry.[3 11] Tobacco smoking is associated with sinonasal squamous cell carcinoma but shows weak and inconsistent association with adenocarcinoma.[12]

Sinonasal adenocarcinoma is a rare disease and despite the large population and the more than 1.5 million accumulated person-years, the small number of cases is a limitation as reflected by the wide CIs. But the rarity of the disease may also be a strength because it is expected to reflect rare causes and thus the potential for large effect estimates.[6]

In conclusion, this study suggests an increased risk of sinonasal adenocarcinoma following styrene exposure. The observations are, however, few, confounding from wood dust exposure cannot be ruled out, and additional studies are needed before firm conclusions can be drawn.

Contributors MSN conducted analysis and interpretation of data and drafted the work. All authors designed the work, interpreted data, revised it for intellectual content and provided final approval for the work to be published and agreed to be accountable for all aspects of the work.

Funding The study is funded by the Danish Council for Independent Research (grant no. 6110-00197) and the Danish Working Environment Research Fund (grant no. 32-2011-09).

Competing interests None declared.

Patient consent Not required.

Ethics approval The Danish Data Protection Agency approved the study (j.no: 1-16-02-01-07). In Denmark, register studies and individual surveys, where biological materials are not included, do not need approval from the Committee System on Biomedical Research Ethics. Participants in the survey were informed of the possibility to withdraw their consent of participation at any point in time.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Acheson ED, Cowdell RH, Hadfield E, *et al*. Nasal cancer in woodworkers in the furniture industry. *Br Med J* 1968;2:587–96.
2 Demers PA, Kogevinas M, Boffetta P, *et al*. Wood dust and sino-nasal cancer: pooled reanalysis of twelve case-control studies. *Am J Ind Med* 1995;28:151–66.
3 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Arsenic, metals, fibres, and dusts. *IARC Monogr Eval Carcinog Risks Hum* 2012;100(Pt C):11–465.
4 Waldron HA. A brief history of scrotal cancer. *Br J Ind Med* 1983;40:390–401.
5 Creech JL, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 1974;16:150–1.
6 Rothman KJ. Causes. *Am J Epidemiol* 1976;104:587–92.
7 Christensen MS, Hansen J, Ramlau-Hansen CH, *et al*. Cancer incidence in workers exposed to styrene in the Danish-reinforced plastics industry, 1968–2012. *Epidemiology* 2017;28:300–10.
8 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. *IARC Monogr Eval Carcinog Risks Hum* 2002;82:1–556.
9 Christensen MS, Vestergaard JM, d'Amore F, *et al*. Styrene exposure and risk of lymphohematopoietic malignancies in 73,036 reinforced plastics workers. *Epidemiology*. In Press.
10 National Academy of Sciences. *Committee to review the styrene assessment in the national toxicology program 12th report on carcinogens, board on environmental studies and toxicology, division on earth and life studies, national research council*. Washington (DC): National Academy of Sciences, 2014.
11 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum* 2012;100(Pt F):9–562.
12 't Mannetje A, Kogevinas M, Luce D, *et al*. Sinonasal cancer, occupation, and tobacco smoking in European women and men. *Am J Ind Med* 1999;36:101–7.

Sinonasal adenocarcinoma following styrene exposure in the reinforced plastics industry

Mette Schou Nissen, Zara Ann Stokholm, Mette Skovgaard Christensen, Vivi Schlünssen, Jesper Medom Vestergaard, Inge Brosbøl Iversen and Henrik Albert Kolstad

Occup Environ Med published online March 14, 2018

ORIGINAL ARTICLE

Cancer mortality in an international cohort of reinforced plastics workers exposed to styrene: a reanalysis

Dana Loomis,[1,2] Neela Guha,[1] Manolis Kogevinas,[3,4,5,6] Vincenzo Fontana,[7] Valerio Gennaro,[7] Henrik A Kolstad,[8] Damien Martin McElvenny,[9] Markku Sallmén,[10] Rodolfo Saracci[1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2018-105131).

[1]International Agency for Research on Cancer, Lyon, France
[2]University of Nevada, Reno, Reno, Nevada, USA
[3]ISGlobal, Barcelona, Spain
[4]CIBER Epidemiologia y Salud Pública (CIBERESP), Barcelona, Spain
[5]Universitat Pompeu Fabra (UPF), Barcelona, Spain
[6]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
[7]Policlinico San Martino, IRCCS Scientific Institute for Research and Care in Oncology, Genova, Italy
[8]Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark
[9]Insitute of Occupational Medicine, Edinburgh, UK
[10]Centre of Expertise for Health and Work Abili, Finnish Institute of Occupational Health, Helsinki, Finland

Correspondence to
Professor Dana Loomis, International Agency for Research on Cancer, Lyon 69008, France; loomisd@iarc.fr

Received 14 March 2018
Revised 15 March 2018
Accepted 18 March 2018

To cite: Loomis D, Guha N, Kogevinas M, *et al*. *Occup Environ Med* Epub ahead of print: [please include Day Month Year]. doi:10.1136/oemed-2018-105131

ABSTRACT

Objective To investigate the carcinogenicity of styrene by reanalysing data from a previous international cohort study of workers in the reinforced plastics industry.

Methods Mortality from cancers of prior interest was analysed with more detailed consideration of exposure–response relations and an updated classification of leukaemias and lymphomas in data from a previous international cohort study of 37 021 reinforced plastics workers exposed to airborne styrene.

Results Increased mortality from non-Hodgkin's lymphoma (NHL) was associated with the mean level of exposure to styrene in air (relative risk (RR) 2.31, 95% CI 1.29 to 4.12 per 100 ppm), but not with cumulative styrene exposure. Similar associations with mean exposure were observed for the oesophagus (RR 2.44, 95% CI 1.11 to 5.36 per 100 ppm) and pancreas (RR 1.89, 95% CI 1.17 to 3.09). Oesophageal cancer mortality was also associated with cumulative styrene exposure lagged 20 years (RR 1.16, 95% CI 1.03 to 1.31). No other cancer, including lung cancer, was associated with any indicator of styrene exposure.

Conclusion This reanalysis does not substantially change the conclusions of the original study with respect to NHL or lung cancer but new evidence concerning cancers of the oesophagus and pancreas merits further investigation.

Key messages

What is already known about this subject?
- Styrene is classified as a possible carcinogen based on associations with leukaemia and lymphoma in previous studies.
- Recent studies suggest positive associations with several other cancers, including lung cancer.

What are the new findings?
- Among reinforced plastics workers, mortality from non-Hodgkin's lymphoma was associated with career mean styrene exposure, but not with cumulative styrene exposure.
- Cancer of the oesophagus was significantly associated with cumulative and mean styrene exposure.
- Cancer of the pancreas was significantly associated with mean styrene exposure.
- Mortality from myeloid leukaemia was not significantly associated with any measure of styrene exposure, nor was lung cancer mortality.

How might this impact on policy or clinical practice in the foreseeable future?
- The carcinogenicity of styrene merits further investigation taking into account these new findings.

INTRODUCTION

Styrene is a common industrial chemical that is produced worldwide in large volumes and is used in making plastic products, foams, resins and synthetic rubber.[1] Occupational exposure to styrene can occur in industries producing or using it, while the population at large may be exposed to styrene at lower concentrations as a component of air pollution and of cigarette smoke and as a food contaminant.[2]

Investigations into the potential carcinogenicity of styrene were prompted by reports in the 1970s and 1980s of excess leukaemia and lymphoma among workers in styrene production and polymerisation and styrene-butadiene rubber manufacturing facilities.[3–6] Following these initial reports, further epidemiological studies focusing on cancers of the haematolymphatic system were undertaken in those industries (eg, refs.[7–9]) and in the reinforced plastics industry,[10–12] where styrene exposures were high and few other known or suspected carcinogens were believed to be present.

Based on observations of positive associations between exposure to styrene and diverse cancers of lymphatic and haematopoietic tissues in several of these epidemiological studies and on experimental findings, styrene was subsequently classified as 'possibly carcinogenic to humans' (group 2B) by the International Agency for Research on cancer[2] and as 'reasonably anticipated to be a human carcinogen' in the US Report on Carcinogens.[13]

Subsequent to those evaluations, further analyses of several cohorts exposed to styrene have reported increased risks of other cancers, notably lung cancer.[14–19] In addition, the understanding of the leukaemias and lymphomas has changed considerably, with multiple myeloma and the acute

and chronic lymphoid leukaemias now classified as subtypes of non-Hodgkin's lymphoma (NHL).[20]

To investigate the extent to which leukaemia, NHL, as currently defined, and cancers of the lung and several other sites might be associated with occupational exposure to styrene, we reanalysed data from a large international cohort study of glass-reinforced plastics workers[12] with a more detailed consideration of latency and exposure–response relations. The last analysis of this cohort published in 1994 showed a statistically significant trend in mortality from all lymphatic and haematopoietic cancers combined with increasing mean, but not cumulative, styrene exposure and non-significant increases in mortality from malignant lymphoma, as then defined, with both cumulative and mean styrene exposure.[12]

METHODS

Study population

In 1988, the International Agency for Research on Cancer (IARC) initiated a study of workers in the reinforced plastics industry in Denmark, Finland, Italy (two centres), Norway, Sweden and the UK (in the UK, two centres) to investigate associations between the risk of tumours of the lymphatic and haematopoietic systems and exposure to styrene. The study population and methods have been described elsewhere.[12] Briefly, workers were enrolled from eight centres encompassing >600 plants. One cohort in the UK had been enumerated and analysed previously,[9] and results from a separate analysis of the Danish cohort were published simultaneously with those of the full international study.[21] In total, 40 668 workers (34 560 men and 6128 women) were included and followed for cancer mortality. The follow-up period averaged 13 years with the dates spanned varying among cohorts, from 1945 at the earliest to 1991 at the latest. In total, about 3% of the cohort was lost to follow-up ranging from <1% in Finland to 7% in one UK centre.

Updated results for the Danish cohort and one British cohort based on extended follow-up have been published recently,[16 17] and we investigated the possibility of updating the follow-up for the other six cohorts. However, this proved to be infeasible principally due to retirements of investigators and loss of records in several centres. In addition, new national privacy protection legislation prohibited the use of existing data from Norway, which had contributed 9% of person-time in the original cohort. Consequently, we reanalysed data from the cohort excluding Norway and did not add new mortality data from the two cohorts whose follow-up had been extended in order to avoid large variations in the time period of observation. Analysis files were reconstructed from the original data and errors were corrected in the process.

Cancer mortality data

The previous analysis of the cohort focused on cancers of lymphatic and haematopoietic tissues, with detailed data presented for all such cancers combined, leukaemias and malignant lymphomas, as defined in the 8th revision of the International Classification of Diseases (ICD). More limited analyses were reported for cancers of the lung, oesophagus, kidney and pancreas.[12]

To update the analysis, we regrouped ICD 8 and 9 codes from the original study to approximate the current WHO classification of the lymphomas and leukaemias,[20] as we did not have access to original diagnostic records (online supplementary table S1). Codes for lymphosarcoma and reticulosarcoma (200), other malignant neoplasms of lymphoid and histiocytic tissue (202), chronic lymphoid leukaemia (204.1) and multiple myeloma (203) were aggregated under the heading of NHL; there were no deaths in the cohort from acute lymphoid leukaemia, which is also considered to be a subtype of NHL. Acute and chronic myeloid leukaemia (ICD 8/9 205.0 and 205.1, respectively) were combined for analysis because of small numbers. This grouping was done independent of knowledge about exposure status of any individuals in the cohort.

In addition, we conducted internal exposure–response analyses for the other specific cancers considered in the previous analyses and for cancers of the bladder and prostate, which showed positive associations in several recent studies[14–19 22] and had at least 10 deaths among exposed workers.

Exposure assessment

The study plants, most of which were small, produced a variety of reinforced plastic products including boats, tanks, containers, panels and small pieces, such as helmets, by laminating fibres with resins containing styrene. Workers were assigned to mutually exclusive groups based on their longest-held jobs. Laminators, production workers with mixed tasks or in small plants with no fixed job titles and workers who regularly entered areas where styrene was handled but were not involved in manual lamination were classified as exposed to styrene. Other manual and clerical personnel who worked in the industry but were not regularly exposed to styrene were classified as unexposed. The duration of exposure was estimated as the time employed in exposed jobs, which may have begun after the start of employment. Information on job titles and tasks was not available in Denmark, so all workers in that subcohort were assigned to an unspecified job category presumed to involve exposure to styrene.

Quantitative exposure to styrene was estimated from approximately 11 600 personal measurements of styrene in air in the years 1970–1990. In those cases when multiple measurements were available for a worker, they were combined to estimate the time-weighted average. Mean styrene concentrations were estimated according to country, job, product and time period and entered into a job-exposure matrix (JEM), which was then linked to full individual work histories. An analysis of about 18 000 measurements of mandelic and phenoglyoxylic acid, the main styrene metabolites in urine, supported the development of the JEM.[23] Because exposure data for years before 1970 were only available for Denmark, exposures in other countries during earlier years were estimated by extrapolation.[12] In those countries, the average styrene concentration was assumed to have been 200 ppm, as observed in Denmark, until 1965 and then to decline linearly to the arithmetic mean of the earliest measurements in each country.

Data analysis

We analysed associations of mortality from the selected cancers with indicators of exposure to styrene using the ungrouped form of Poisson regression, equivalent to the discrete-time hazard model[24 25] to estimate adjusted rate ratios (RRs) and likelihood-based 95% CIs. Follow-up time was treated as the time axis, with each observation representing one person-year of experience or a fraction thereof in the case of censoring during the year. For each type of cancer, we first evaluated demographic and occupational predictors including age at risk, calendar time, sex, country, length of follow-up and time since first exposure. to develop a base model that best fit the mortality data as assessed by the Akaike information criterion (AIC). Age, calendar time, sex and country were entered in categorical form, while length

of follow-up and time since first exposure were treated as continuous linear variables. We evaluated the effect of each covariate on the association of cancer mortality with styrene exposure and any that appreciably changed the RR were retained. Different covariates could thus be selected according to the outcome, resulting in a final model that estimated parameters for indicators of exposure to styrene adjusted for those factors.

The exposure indicators evaluated included employment in exposed jobs, employment as a laminator (the job with the highest average exposure to styrene), duration in exposed jobs, cumulative styrene exposure (ppm-years) and mean styrene concentration (ppm) in exposed jobs. Cumulative and mean styrene exposure were entered as continuous variables assuming a model of form $ln(\mathrm{RR}) = \beta X + \gamma \boldsymbol{P}$ in which the natural log of the RR is linearly related to the level of styrene exposure, X, and a vector of other demographic and occupational predictor variables, P. To investigate potential latency effects, we evaluated cumulative and mean exposure lagged by 0, 5, 10 and 20 years for lymphohaematopoietic cancers and by 0, 10 and 20 years for other cancers.

To further investigate the shape of the exposure–response function for lung cancer, which had the largest number of deaths, we conducted additional analyses in which exposure was smoothed with penalised splines. The fit of alternative models was assessed using the likelihood ratio χ^2 for the exposure terms.

Analyses using log-linear models were performed in Stata and models using smoothed terms were fit in R.[26]

RESULTS

Descriptive data for the full cohort, including Norway, have already been published[12] and have not substantially changed. After reconstructing the analysis files, correcting errors and excluding data from Norway, this reanalysis included 37 021 workers, who contributed approximately 506 459 person-years of follow-up experience, during which 2351 had died. In the cohort with Norway excluded, the mean duration of employment was 3.1 years and workers spent an average of 2.2 years in jobs exposed to styrene. The arithmetic mean concentration of styrene during employment in these jobs was approximately 63 ppm, resulting in an arithmetic mean cumulative exposure of about 158 ppm-years per worker (table 1). Exposed and unexposed workers within the cohort had similar mortality for all causes and all cancer (RR 1.01, 95% CI 0.89 to 1.14 and 1.01, 95% CI 0.81 to 1.17, respectively) (online supplementary table S2).

Mortality rates for the cancers of prior interest were not significantly increased among all workers who held jobs involving exposure to styrene compared with unexposed workers (table 2). RRs were 3.50 (95% CI 0.46 to 26.82) and 1.85 (95% CI 0.81 to 6.15) for oesophageal cancer and prostate cancer, respectively, and near or below unity for all other cancers, including NHL and myeloid leukaemia.

Among laminators, RRs were elevated for cancer of the oesophagus (RR 2.71, 95% CI 1.00 to 7.37), pancreas (RR 1.18, 95% CI 0.53 to 2.61) and prostate (RR 1.85, 95% CI 0.64 to 5.36).

Mortality from NHL (RR 1.40, 95% CI 0.51 to 3.79) and cancer of the pancreas (RR 2.12, 95% CI 0.93 to 4.38) was increased among workers employed 2 to <5 years in exposed jobs relative to workers exposed for <2 years (table 2), but no consistent increase in mortality from those cancers was observed among workers exposed >5 years. Oesophageal cancer mortality was increased in workers exposed for ≥2 years (RR 1.80, 95% CI 0.62 to 45.22), but there were too few deaths for analysis of longer exposure duration. Mortality from cancers of the lung (RR 1.14, 95% CI 0.80 to 1.62) and prostate (RR 1.35, 95% CI 0.57 to 3.16) was increased only among workers employed ≥5 years. For lung cancer, which had the largest number of deaths (231), we also considered longer exposure durations of 5 to <10, 10 to <20 and ≥20 years; the RRs in these categories were 1.02 (95% CI 0.65 to 1.60), 1.29 (95% CI 0.77 to 2.15) and 1.56 (95% CI 0.49 to 4.97), respectively. There were no significant trends in mortality from any cancer with the duration of exposure to styrene (table 2). For cancers of the kidney and bladder, the RRs for all of the exposure metrics considered were near unity or below.

We analysed exposure–response relationships of styrene with mortality from total NHL (including multiple myeloma), multiple myeloma, myeloid leukaemia and lung cancer, which were of prior interest, and with cancers of the oesophagus, pancreas and prostate, as they had adequate numbers for analysis and indications of associations with employment in exposed jobs and exposure duration.

For NHL, the RR was 1.02 or 1.03 per 100 ppm-years of cumulative exposure to styrene for lag periods of 0, 5 and 10 years and was not statistically significant (table 3). However, NHL mortality was significantly associated with mean styrene concentration in exposed jobs (RR 2.31, 95% CI 1.29 to 4.12 per 100 ppm with a 0-year lag). Multiple myeloma was non-significantly associated with cumulative styrene exposure with a 10-year lag and with mean styrene exposure for all lag intervals (table 3). Myeloid leukaemia was not associated with cumulative styrene exposure, while RRs were non-significantly increased with increasing mean exposure (table 3).

Table 1 International Agency for Research on Cancer cohort of reinforced plastics workers exposed to styrene, 1945–1991, cohort characteristics

	N	%*	Person-years
All workers	37 021	100	506 459
Men	31 692	85	428 006
Women	5692	15	78 453
Exposed job	31 803	85	407 459
Laminators	8946	24	132 062
Unexposed job	3797	11	66 412
Unknown job	1833	5	32 705
Employment duration (years)			
<2	22 865	62	307 521
2 to <5	5583	15	82 698
≥5	7086	19	95 895
Unknown	1487	4	20 345
Exposure duration (years)			
<2	24 715	67	339 328
2 to <5	4593	12	64 646
≥5 y	5075	14	61 514
Unknown	2638	7	40 971
	Mean	**Range**	
Mean employment duration (years)	3.1	<0.01–62.0	
Mean exposure duration (years)	2.2	0–33.5	
Mean length of follow-up (years)	12.8	0–45.0	
Mean styrene exposure (ppm)	63.1	0–205.0	
Mean cumulative styrene exposure (ppm-years)	158.0	0–4543.1	

*Per cents may not add to 100 because of rounding.

Table 2 Cancer mortality by job and exposure duration, International Agency for Research on Cancer cohort of reinforced plastics workers exposed to styrene, 1945–1991

Cancer (number of deaths)	Unexposed jobs*		Exposed jobs			Laminators			Exposed <2years		Exposed 2<5 years			Exposed≥5 years			P-trend†
	N	RR	N	RR‡	95% CI‡	N	RR	95% CI	N	RR	N	RR	95% CI	N	RR	95% CI	
NHL (29)§	5	1.00	22	1.01	0.37 to 2.74	6	0.98	0.40 to 2.42	17	1.00	5	1.40	0.51 to 3.79	5	0.92	0.34 to 2.54	0.78
Multiple myeloma (8)	2	1.00	8	1.05	0.20 to 5.37	0	0	–	7	1.00	3¶	0.77	0.20 to 3.00	1	–	–	0.23
Myeloid leukaema (15)**	2	1.00	12	0.57	0.09 to 3.49	1	0.19	0.01 to 3.49	10	1.00	4¶	0.53	0.14 to 1.94	3	–	–	0.53
Lung (231)	48	1.00	159	0.85	0.57 to 1.19	49	0.88	0.62 to 1.25	144	1.00	26	0.94	0.62 to 1.42	42	1.14	0.80 to 1.62	0.43
Oesophagus (16)	1	1.00	15	3.50	0.46 to 26.82	7	2.71	1.00 to 7.37	8	1.00	6¶	1.80	0.62 to 5.22	4	–	–	0.20
Pancreas (35)	7	1.00	27	1.06	0.46 to 2.46	8	1.18	0.53 to 2.61	19	1.00	8	2.12	0.93 to 4.38	7	1.33	0.56 to 3.19	0.65
Bladder (25)	3	1.00	21	0.92	0.22 to 3.80	3	0.88	0.22 to 3.50	18	1.00	3	0.72	0.21 to 2.46	3	0.54	0.15 to 1.94	0.57
Kidney (13)	2	1.00	9	0.83	0.18 to 3.99	3	0.88	0.21 to 3.71	7	1.00	4¶	1.08	0.31 to 3.78	2	–	–	0.90
Prostate (33)	5	1.00	27	1.85	0.64 to 5.36	5	1.36	0.47 to 3.89	22	1.00	4	0.92	0.32 to 2.70	7	1.35	0.57 to 3.16	0.77

*Missing and unknown jobs excluded.
†P for continuous linear variable.
‡RRs adjusted as follows: NHL, lung cancer, bladder cancer: age, calendar decade, country, sex; multiple myeloma: age, calendar decade, sex; myeloid leukaemia: age, sex, country; kidney cancer: age, calendar decade, sex; prostate cancer: age, country; pancreatic cancer, oesophageal cancer: age.
§Includes multiple myeloma.
¶Exposure duration ≥2 years.
**Includes acute and chronic myeloid leukaemia.
NHL, non-Hodgkin's lymphoma; RR, rate ratio.

Lung cancer mortality was not associated with any quantitative measure of styrene exposure (table 4). Mortality from oesophageal cancer was significantly associated with cumulative styrene and mean styrene exposure lagged 20 years (RRs 1.16, 95% CI 1.03 to 1.31 per 100 ppm-years and RR 3.36, 95% CI 1.74 to 6.49 per 100 ppm, respectively). Mortality from cancer of the pancreas increased significantly with unlagged mean styrene exposure (RR 1.89, 95% CI 1.17 to 3.06 per 100 ppm), but not with cumulative exposure. Mortality from cancer of the prostate showed a similar pattern of a non-significant increase with higher unlagged mean exposure, but no association with cumulative exposure (table 4).

For lung cancer mortality and cumulative exposure to styrene, we also investigated the shape of the exposure–response function using non-parametric spline models. These models did not fit the data better, as assessed by AIC, than parametric models with cumulative exposure entered as a linear term, however (illustrative data shown in online supplementary figure S1).

We conducted additional analyses to assess the effects on the results of uncertainties in estimating exposure to styrene. To gauge potential misclassification due to the lack of detailed occupational histories for workers in Denmark, we repeated the principal analyses excluding that subcohort. To evaluate potential bias due to the lack of quantitative exposure data for years before 1970 in countries other than Denmark, we performed two additional exposure–response analyses. One used alternative exposure estimates based on an assumption that styrene concentrations in the period when no data were available were equal to the earliest measured concentrations in each country[12] and another included only workers first exposed after 1970. Among the latter group of workers first exposed in later years, lung cancer mortality was significantly associated with cumulative styrene exposure (RR 1.11, 95% CI 1.02 to 1.20) and non-significantly increased with mean exposure (RR 1.26, 95% CI 0.76 to 2.07). None of the other analyses gave results materially different from those based on the full cohort or the primary exposure model for any cancer, although the exclusions reduced the precision of most risk estimates (online supplementary table S3).

DISCUSSION

In this reanalysis of an international cohort of workers exposed to styrene in the glass-reinforced plastics industry, mortality

Table 3 Mortality from lymphohaematopoietic cancers and estimated exposure to styrene, International Agency for Research on Cancer cohort of reinforced plastics workers exposed to styrene, 1945–1991

	NHL (n=24)			Multiple myeloma (n=8)			Myeloid leukaemia* (n=15)		
	RR†	95% CI†	AIC	RR	95% CI	AIC	RR	95% CI	AIC
Cumulative styrene exposure (100 ppm-years)									
0-year lag	1.02	0.94 to 1.10	488.2	0.82	0.54 to 1.26	179.7	0.90	0.73 to 1.10	314.6
5-year lag†	1.02	0.94 to 1.11	488.2	0.87	0.59 to 1.27	180.3	0.91	0.73 to 1.12	315.1
10-year lag	1.03	0.94 to 1.12	488.1	1.69	0.30 to 1.62	179.5	0.88	0.66 to 1.17	315.0
Mean styrene exposure (100 ppm)									
0-year lag	2.31	1.29 to 4.12	480.3	1.86	0.71 to 4.86	179.6	0.92	0.37 to 2.32	316.1
5-year lag†	2.29	1.33 to 3.93	479.6	2.25	0.92 to 5.48	178.1	1.34	0.61 to 2.94	315.6
10-year lag	1.78	1.05 to 3.02	484.2	1.31	0.48 to 3.58	180.9	1.50	0.71 to 3.17	315.1

*Includes acute myeloid leukaemia and chronic myeloid leukaemia.
†RR per 100 ppm-year or 100 ppm; RRs adjusted as follows: NHL, multiple myeloma, age, calendar decade, sex; myeloid leukaemia, age, calendar year, sex, country.
AIC, Akaike information criterion; NHL, non-Hodgkin's lymphoma; RR, rate ratio.

Table 4 Cancer mortality and estimated exposure to styrene, International Agency for Research on Cancer cohort of reinforced plastics workers exposed to styrene, 1945–1991

	Lung			Oesophagus			Pancreas			Prostate		
	RR*	95% CI	AIC	RR	95% CI	AIC	RR	95% CI	AIC	RR	95% CI	AIC
Cumulative styrene exposure (100 ppm-years)												
0-year lag	1.02	0.99 to 1.05	3099	1.06	0.97 to 1.16	298.6	1.03	0.97 to 1.10	612.4	1.03	0.96 to 1.10	538.5
10-year lag	1.03	0.99 to 1.06	3099	1.08	0.98 to 1.19	298.2	1.03	0.96 to 1.11	612.6	1.00	0.92 to 1.10	539.2
20-year lag	1.00	0.91 to 1.09	3100	1.16	1.03 to 1.31	296.8	1.01	0.84 to 1.22	613.2	0.97	0.76 to 1.23	539.2
Mean styrene exposure (100 ppm)												
0-year lag	0.98	0.79 to 1.22	3100	2.44	1.11 to 5.36	294.8	1.89	1.17 to 3.06	606.4	1.26	0.76 to 2.11	538.3
10-year lag	0.97	0.80 to 1.18	3100	2.53	1.30 to 4.90	293.0	1.31	0.82 to 2.10	611.9	1.03	0.64 to 1.68	539.2
20-year lag	0.81	0.59 to 1.12	3101	3.36	1.74 to 6.49	290.9	1.14	0.57 to 2.28	613.1	1.07	0.55 to 2.10	539.2

*RR per 100 ppm-year or 100 ppm. RRs adjusted as follows: NHL, age, calendar decade, sex; lung cancer, age, sex, country; oesophageal cancer, pancreatic cancer: age; prostate cancer: age, country.
AIC, Akaike information criterion; NHL, non-Hodgkin's lymphoma; RR, rate ratio.

from NHL and cancers of the oesophagus, pancreas and prostate showed associations with the employment in exposed jobs or the duration of such employment, but effect estimates were imprecise and trends with duration were not statistically significant.

Increased mortality from lympohaematopoietic cancers, including NHL, has also been reported in several industrial cohorts[3–11] as well as a previous analysis of this cohort which showed associations with the metrics of time since first exposure and average level of exposure to styrene, but not with duration of exposure or cumulative exposure.[12] However, these prior studies used various definitions of NHL that have been superseded by the current WHO definition. In this reanalysis, NHL was defined by regrouping ICD codes for lymphomas and leukaemias from the original study following the current WHO classification, which now includes multiple myeloma and acute and chronic lymphatic leukaemia.[20] We did not have the detailed information needed to identify B-cell and T-cell lymphomas or other NHL subtypes that did not have codes in the 8th and 9th revisions of the ICD. This regrouping yielded associations of styrene exposure and NHL mortality that were essentially similar to those in the original analysis of the cohort.[12]

We found statistically significant associations of oesophageal cancer with cumulative and mean styrene exposure and of pancreatic cancer with mean styrene exposure that were not seen in the less detailed exposure–response analysis in the previous paper.[12]

No clear increase in mortality from lung or bladder cancer with exposure to styrene was observed in this reanalysis or in the original analysis,[12] but we did find increased lung cancer risk among workers employed >10 years and among those hired after 1970. Excess risk of lung and bladder cancers has been reported in other studies,[7 14 15 19 22] including in updated data for components of this cohort from Denmark and the UK.[16 17] Given that these reports were based on extended follow-up of cohorts enumerated around the same time as the one we studied, it is possible that longer follow-up is needed to observe any increase in lung cancer mortality.

Inconsistencies in reported results between publications may be due to several factors. Some previous studies may have been underpowered to detect an effect as they examined cancer mortality in industries where levels of exposure to styrene are fairly low. Furthermore, co-exposures to known or suspected carcinogens may have occurred, resulting in spurious findings. For example, workers in the styrene-butadiene rubber industry may have significant exposures to 1,3-butadiene, while workers involved in styrene production and polymerisation may be exposed to diverse chemicals, including benzene.[5 7] Benzene and 1,3-butadiene are recognised causes of leukaemia, and positive associations with NHL have been seen in some studies.[27]

A strength of this study is that it was based on observations of >37 000 workers, most of whom were exposed to styrene without significant exposures to other carcinogens. Acetone is the most frequent chemical co-exposure encountered in the reinforced plastics industry,[28] but is not known or suspected to be carcinogenic.[29] The presence of dichloromethane (arithmetic mean concentration 51 mg/m^3) was reported in a study of Danish industries, including reinforced plastics, that used styrene in the period 1955–1988; perchloroethylene and trichloroethylene were also detected in a small number of samples, but the concentrations were very low.[28] Styrene 7,8-oxide has been detected more recently in the air of reinforced-plastic manufacturing workshops,[30] but no measurements were available for the facilities included in this study. Workers involved in the lamination process may also have been exposed to man-made fibres, including continuous glass filaments; although no data on exposure levels were available for the cohort, previous studies have not demonstrated a link with cancer.[31]

Moreover, several previous studies were unable to account for potential confounding by non-occupational risk factors, notably tobacco smoking, as no information was collected at the individual level and analyses were based on SMRs with the general population as a referent group. Although information on tobacco smoking and other personal risk factors was also lacking for our international cohort, concerns about potential confounding by non-occupational risk factors are reduced in our analyses with an internal referent group of unexposed or less exposed workers.

Other limitations of this study include the deletion of data from Norway, which modestly reduced precision for some estimates, the relatively short duration of employment in the industry and of follow-up (approximately 3 and 13 years, respectively, on average) and small numbers of deaths for some of the cancers of interest. Approximately 60% workers in our study were employed <2 years, reflecting the typical employment pattern in the industry.[12] The observed tendency for several cancers to be associated with mean, but not cumulative styrene exposure may be related to the short duration of exposure for most workers, which would minimise contrast in cumulative exposure. Given the high proportion of short-term workers, healthy worker survivor bias could be a potential explanation for the observation that the risk estimates for NHL and cancers of the pancreas and prostate were higher in workers who were exposed to styrene 2–5 years relative to those exposed for ≥5 years.

It is also possible that some risk estimates were affected by exposure measurement error. Because all workers in Denmark were assigned to an unspecified job category presumed to involve exposure to styrene, up to one-fourth of the workers classified as styrene exposed may have actually been unexposed. However, analyses excluding Denmark gave similar results, so the impact of this potential source of error appears to have been minimal. It is also possible that heavily exposed short-term workers were excluded from the cohort because early payroll records (used to classify workers with respect to styrene exposure) were not available from all of the 660 plants for various reasons.[12] The estimation of exposure before 1970 by extrapolating from measurements in Denmark is another potential source of information bias. If the actual exposures during that time were higher than the extrapolated estimates, then estimated RRs would be biased towards the null, while if they were lower, the RRs would be biased upwards.

CONCLUSION

This reanalysis using a modern definition of NHL and a more detailed analytical approach does not substantially change the conclusions of the original study with respect to the associations of NHL and lung cancer with exposure to styrene: NHL mortality was associated with mean career styrene exposure, while lung cancer was not associated with any indicator of styrene exposure in the full cohort. However, we found suggestive new evidence that increased mortality from cancer of the pancreas is associated with employment in exposed jobs and with average styrene concentration and that cancer of the oesophagus is associated with cumulative styrene exposure, as well as with these indicators. More information about the associations of these cancers with exposure to styrene would be valuable in light of the inconsistent results of other studies. A full update of cancer mortality in this cohort would be informative, but may not be feasible. New studies and updated analyses of populations occupationally and environmentally exposed to styrene are therefore warranted. Ideally, such studies would be based on cancer incidence data, which would improve the identification and classification of leukaemias and lymphomas.

Correction notice This article has been corrected since it first published online. It is no longer open access.

Acknowledgements The authors gratefully acknowledge Tom Bellander, Marco Biocca, David Coggon, Claudia Galassi and Allan Astrup Jensen for their contributions to the original study and their reading of this paper.

Contributors DL and NG performed the data analysis and drafted the papers. All other authors contributed to data collection and critically reviewed the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Ethics approval This study was cleared by the IARC Ethics Committee as not presenting any potential ethical implications because it analyses deidentified historical data and reports aggregate statistical results.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

1 International Styrene Industry Forum (ISF). The styrene forum. 2017 http://www.styreneforum.org/index.html (accessed 24 Nov 2017).
2 International Agency for Research on Cancer. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2002:82.
3 Hodgson JT, Jones RD. Mortality of styrene production, polymerization and processing workers at a site in northwest England. *Scand J Work Environ Health* 1985;11:347–52.
4 Meinhardt TJ, Lemen RA, Crandall MS, *et al*. Environmental epidemiologic investigation of the styrene-butadiene rubber industry. Mortality patterns with discussion of the hematopoietic and lymphatic malignancies. *Scand J Work Environ Health* 1982;8:250–9.
5 Nicholson WJ, Selikoff IJ, Seidman H. Mortality experience of styrene-polystyrene polymerization workers. Initial findings. *Scand J Work Environ Health* 1978;4(Suppl 2):247–52.
6 Ott MG, Kolesar RC, Scharnweber HC, *et al*. A mortality survey of employees engaged in the development or manufacture of styrene-based products. *J Occup Med* 1980;22:445–60.
7 Bond GG, Bodner KM, Olsen GW, *et al*. Mortality among workers engaged in the development or manufacture of styrene-based products–an update. *Scand J Work Environ Health* 1992;18:145–54.
8 Matanoski GM, Santos-Burgoa C, Schwartz L. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). *Environ Health Perspect* 1990;86:107–17.
9 Coggon D, Osmond C, Pannett B, *et al*. Mortality of workers exposed to styrene in the manufacture of glass-reinforced plastics. *Scand J Work Environ Health* 1987;13:94–9.
10 Okun AH, Beaumont JJ, Meinhardt TJ, *et al*. Mortality patterns among styrene-exposed boatbuilders. *Am J Ind Med* 1985;8:193–205.
11 Wong O. A cohort mortality study and a case-control study of workers potentially exposed to styrene in the reinforced plastics and composites industry. *Br J Ind Med* 1990;47:753–62.
12 Kogevinas M, Ferro G, Andersen A, *et al*. Cancer mortality in a historical cohort study of workers exposed to styrene. *Scand J Work Environ Health* 1994;20:251–61.
13 National Toxicology Program (NTP). 12th report on carcinogens. *Rep carcinog* 2011;12.
14 Sathiakumar N, Delzell E. A follow-up study of mortality among women in the North American synthetic rubber industry. *J Occup Environ Med* 2009;51:1314–25.
15 Sathiakumar N, Brill I, Delzell E. 1,3-butadiene, styrene and lung cancer among synthetic rubber industry workers. *J Occup Environ Med* 2009;51:1326–32.
16 Christensen MS, Hansen J, Ramlau-Hansen CH, *et al*. Cancer incidence in workers exposed to styrene in the danish-reinforced plastics industry, 1968-2012. *Epidemiology* 2017;28:300–10.
17 Coggon D, Ntani G, Harris EC, *et al*. Risk of cancer in workers exposed to styrene at eight British companies making glass-reinforced plastics. *Occup Environ Med* 2015;72:165–70.
18 Collins JJ, Bodner KM, Bus JS. Cancer mortality of workers exposed to styrene in the U.S. Reinforced plastics and composite industry. *Epidemiology* 2013;24:195–203.
19 Ruder AM, Meyers AR, Bertke SJ. Mortality among styrene-exposed workers in the reinforced plastic boatbuilding industry. *Occup Environ Med* 2016;73:97–102.
20 Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, *et al*. eds. *WHO Classification of tumours of haematopoietic and lymphoid tissues*. 4th edn. Lyon: IARC, 2017.
21 Kolstad HA, Lynge E, Olsen J, *et al*. Incidence of lymphohematopoietic malignancies among styrene-exposed workers of the reinforced plastics industry. *Scand J Work Environ Health* 1994;20:272–8.
22 Ruder AM, Bertke SJ. Cancer incidence among boat-building workers exposed to styrene. *Am J Ind Med* 2017;60:651–7.
23 Galassi C, Kogevinas M, Ferro G, *et al*. Biological monitoring of styrene in the reinforced plastics industry in Emilia Romagna, Italy. *Int Arch Occup Environ Health* 1993;65:89–95.
24 Loomis D, Richardson DB, Elliott L. Poisson regression analysis of ungrouped data. *Occup Environ Med* 2005;62:325–9.
25 Richardson DB. Discrete time hazards models for occupational and environmental cohort analyses. *Occup Environ Med* 2010;67:67–71.
26 R Development Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2008.
27 International Agency for Research on Cancer (IARC). A review of human carcinogens, Part F: chemical agents and related occupations. IARC monographs on the evaluation of carcinogenic risks to humans. 2012:100F.
28 Jensen AA, Breum NO, Bacher J, *et al*. Occupational exposures to styrene in Denmark 1955-88. *Am J Ind Med* 1990;17:593–606.
29 Agency for Toxic Substances and Disease Registry (ATSDR). ToxFacts for acetone. https://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=4&tid=1#bookmark06 (accessed 17 Dec 2017).
30 Serdar B, Tornero-Velez R, Echeverria D, *et al*. Predictors of occupational exposure to styrene and styrene-7,8-oxide in the reinforced plastics industry. *Occup Environ Med* 2006;63:707–12.
31 IARC (International Agency for Research on Cancer). Man-made vitreous fibres. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2002:81.

Carcinogenicity of quinoline, styrene, and styrene-7,8-oxide

In March, 2018, a Working Group of 23 scientists from 12 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to finalise their evaluation of the carcinogenicity of quinoline, styrene, and styrene-7,8-oxide. This assessment will be published in Volume 121 of the IARC Monographs.[1]

Quinoline is an azaarene that is present in tobacco smoke and air pollution. Quinoline occurs in petroleum and shale oil processing, and is found in groundwater and soil at coal tar and creosote-contaminated sites. A high production volume chemical, quinoline is used to produce a variety of drugs and dyes. No data were available on cancer in humans, or on exposure, absorption, or distribution of quinoline in humans. In mice and rats, quinoline induced rare tumours of various embryological origins. Malignant tumours were induced with a high incidence at the lowest dose tested, occurred with short latency, and caused early deaths. In both sexes of Crj:BDF1 mice, drinking water exposure to quinoline increased the incidences of liver histiocytic sarcoma, and in various organs, haemangioma and haemangiosarcoma.[2] Additionally, hepatocellular carcinoma incidence was increased in male mice. Quinoline administered by intraperitoneal injection in CD-1 mice induced lymphoma in females and hepatocellular carcinoma in males.[3] In male and female F344/DuCrj rats, drinking water containing quinoline increased the incidences of haemangiosarcoma (in various organs), and hepatocellular adenoma and carcinoma. Nasal cavity sarcoma, nasal esthesioneuroepithelioma, and mediastinal sarcoma were increased in male rats.[2] In three feeding studies,[4] quinoline increased the incidence of liver haemangiosarcoma in male rats of various strains. There was strong evidence that quinoline is genotoxic in experimental systems, inducing mutations[5] and chromosomal damage in rodents and in vitro (upon metabolic activation), but no human data on cancer mechanisms were available. The Working Group classified quinoline as "possibly carcinogenic to humans", Group 2B, based on sufficient evidence of carcinogenicity in experimental animals.

Styrene is present in tobacco smoke and air pollution. A high production volume chemical, styrene is primarily used to produce polystyrene polymers. Styrene and styrene-7,8-oxide, the principal metabolite of styrene in humans, are found in workplace air, particularly in the reinforced plastics and rubber industries.[6] Styrene-7,8-oxide is primarily used to produce epoxy resins.

The most informative epidemiological studies of cancer were in large occupational cohorts (of >100 000 workers) in the reinforced plastics industry, where styrene exposure levels are highest, in Europe,[7] the UK,[8] Denmark,[9] across the USA,[10] and Washington state. The Working Group assessed the overall pattern of the findings for lymphohaematopoietic malignancies as a whole, noting increased incidence or mortality of subtypes of leukaemia and lymphomas in several studies, with greater consistency for leukaemia, and in particular myeloid leukaemia. The incidence of acute myeloid leukaemia increased strongly with increasing cumulative styrene exposure for a latency period of 15 years in the most informative study.[9] Increased myeloid leukaemia (acute and chronic combined) mortality was reported in the US study for the highest cumulative styrene exposure category.[10] There was no overall increased mortality of myeloid leukaemias (acute and chronic combined) in the European cohort, but an increase was observed with increasing mean intensity of exposure in a ten-year lag analysis. The incidence of sinonasal adenocarcinoma, a rare cancer, was increased in one large cohort of reinforced plastics workers,[11] but cases were few and chance and confounding could not be discounted. Evidence for solid tumours, including lung cancer, was sparse or inconsistent. Overall, the epidemiological studies provide credible evidence that exposure to styrene causes lymphohaematopoietic malignancies, but confounding, bias, or chance cannot be ruled out.

In CD-1 mice, inhalation exposure to styrene increased the incidence of bronchioloalveolar carcinoma in males,[12] and in females in a separate study,[13] in which bronchioloalveolar adenoma or carcinoma (combined) was also increased in both sexes. In 020 mice, transplacental exposure followed by gavage increased the incidences of lung carcinoma in females, and lung adenoma or carcinoma (combined) in males and females.[14] In B6C3F1 mice, exposure to styrene by gavage increased the incidence of bronchioloalveolar adenoma or carcinoma (combined) in males, and hepatocellular adenoma in females. In one of two inhalation studies, styrene exposure increased the incidence of malignant mammary tumours in female rats.[15]

The Working Group classified styrene in Group 2A, "probably carcinogenic to humans" based on limited evidence in humans and sufficient evidence in experimental animals for carcinogenicity. Strong evidence of a mechanism that also operates in humans supported the Group 2A classification of styrene. Styrene is rapidly absorbed, widely distributed to adipose tissues, and extensively metabolised in humans and experimental systems. Approximately 60% of excretion products formed from inhaled styrene come from its metabolism to styrene-7,8-oxide. Styrene-7,8-oxide is an electrophile and reacts directly with DNA. There was strong evidence that styrene

Lancet Oncol 2018

Published **Online**
April 18, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30316-4

For more on the **IARC Monographs** see http://monographs.iarc.fr/

Upcoming meetings

June 5–12, 2018, volume 122: Isobutyl nitrite, β-picoline, and some acrylates

Oct 9–16, 2018, volume 123: Some nitro-benzenes and other industrial chemicals

Nov 12–13, 2018: Advisory group to recommend an update to the preamble

IARC Monograph Working Group Members

M Kogevinas (Spain)—Meeting Chair; M Sim (Australia); M E Parent (Canada); G M Calaf (Chile), J Mráz, P Vodicka (Czech Republic); A A Jensen, H Kolstad (Denmark); K Hemminki (Germany); C Colosio (Italy); S Fukushima, T Suzuki (Japan); J P Texeira (Portugal); D H Phillips (UK); S J Bertke, W M Gwinn, D Kriebel, S Nesnow, L A Nylander-French, M Sandy, S L Smith-Roe, G Stoner (unable to attend) (USA)

Declaration of interests
All working group members declare no competing interests.

Invited specialists

R Tornero-Velez (USA)

Declaration of interests
R Tornero-Velez was invited to a workshop with significant travel costs paid by the American Chemistry Council.

Representative

M Sarpa de Campos Mello, for the Ministry of Health, Brazil (unable to attend)

Declaration of interests
All representatives declare no competing interests.

Observers

M I Banton, for the Styrene Information and Research Center (SIRC), USA; T Chachibaia for the NGO 'Ammonium Nitrate Safe Governance Initiative', Georgia (unable to attend); H-P Gelbke, for PlasticsEurope, Belgium; L Vodickova, for the Charles University, Czech Republic; M Wilde, for the University of Kent, UK; J Williamson, for the University of Kent, UK

and styrene-7,8-oxide are genotoxic. In exposed workers, styrene-7,8-oxide-derived DNA adducts were found in the blood[6] and urine, while results were mixed for other indicators of genotoxicity. In human cells in vitro, styrene as well as styrene-7,8-oxide induced DNA damage, gene mutations, chromosomal aberrations, micronucleus formation, and sister-chromatid exchanges;[16] similar findings were seen in various experimental systems. In rodents exposed to styrene or styrene-7,8-oxide, results were equivocal for cytogenetic effects, but positive for DNA damage in multiple tissues.

There was also strong evidence that styrene modulates receptor-mediated effects in exposed human subjects, based on studies reporting increased serum prolactin. Additionally, there was strong evidence that styrene and styrene-7,8-oxide alter cell proliferation. Styrene reduced cell proliferation in cultured human lymphocytes, and styrene and styrene-7,8-oxide increased proliferation in various rodent tissues. In considering the human relevance of the styrene-induced mouse lung tumours, the Working Group reviewed data relevant to a proposed rodent-specific mechanism involving metabolism of styrene to 4-vinylphenol by CYP2F2, cytotoxicity in club (Clara) cells, and regenerative epithelial proliferation in the terminal bronchioles.[17] Styrene induced cytotoxicity, lung cell proliferation, and bronchial hyperplasia in both CD-1 and C57Bl/6 mice, but not in C57Bl/6 Cyp2f2(-/-) mice, or in a C57Bl/6 Cyp2f2(-/-) humanised CYP strain.[12] However, lung tumours developed only in CD-1, and not in C57Bl/6, mice.[12] Furthermore, no in-vivo metabolism data were available in C57Bl/6 strains, and the observed increases in lung cell proliferation did not persist beyond the short term, even with continuous exposure. Thus, the Working Group concluded that the mechanistic events for lung tumour induction by styrene in CD-1, B6C3F1, and 020 mice have not been established.

For styrene-7,8-oxide, there was inadequate evidence of carcinogenicity in humans. In B6C3F1 mice, gavage exposure to styrene-7,8-oxide increased the incidences of forestomach squamous cell papilloma and carcinoma in males and females, and hepatocellular adenoma or carcinoma (combined) in males. Gavage exposure to styrene-7,8-oxide increased the incidences of forestomach squamous cell papilloma and carcinoma in Sprague-Dawley and Fischer 344/N rats of both sexes,[15,18] and mammary benign or malignant (combined) tumours in male Sprague-Dawley rats.[15] In BDIV rats, transplacental exposure to styrene-7,8-oxide followed by gavage increased the incidences of forestomach papilloma in males and forestomach carcinoma in males and females.[19] The Working Group classified styrene-7,8-oxide as "probably carcinogenic to humans" (Group 2A) based on sufficient evidence of carcinogenicity in experimental animals and strong evidence that styrene-7,8-oxide, an electrophile, forms DNA adducts and is genotoxic, a mechanism that also operates in humans.

Rogelio Tornero-Velez was invited to a workshop with significant travel costs paid by the American Chemistry Council. All other authors declare no competing interests.

IARC Monographs Vol 121 Group
International Agency for Research on Cancer, Lyon, France

Declaration of interests
M I Banton is employed by a company that manufactures styrene. Her expenses for attendance at the IARC Monograph Meeting were paid by an industry group with an interest in styrene (Styrene Information and Research Center [SIRC]). H-P Gelbke works as a consultant to the Styrenics Steering Committee (SSC) of PlasticsEurope of the European Chemical Industry Council (CEFIC) and receives funds for it. J Williamson receives research funding from the UK Arts and Humanities Research Council. All other observers declare no competing interests.

IARC Secretariat
L Benbrahim-Tallaa (unable to attend); V Bouvard; T Driscoll; M Foerster; F El Ghissassi; Y Grosse; N Guha; KZ Guyton; A Hall; C Jaillet; H Mattock; D Middleton; K Straif; M Talibov; N Vilahur

Declaration of interests
All secretariat declare no competing interests.

For the **Preamble to the IARC Monographs** see http://monographs.iarc.fr/ENG/Preamble/index.php

For **IARC declarations of interests** see http://monographs.iarc.fr/ENG/Meetings/vol121-participants.pdf

References

1 International Agency for Research on Cancer. Volume 121: Styrene, styrene-7,8-oxide, and quinoline. IARC Working Group. Lyon, France; 20–27 March, 2018. *IARC Monogr Eval Carcinog Risks Hum* (in press).

2 Matsumoto M, Kano H, Suzuki M, et al. Carcinogenicity of quinoline by drinking-water administration in rats and mice. *J Toxicol Sci* 2018; **43:** 113–27.

3 LaVoie EJ, Shigematsu A, Rivenson A. The carcinogenicity of quinoline and benzoquinolines in newborn CD-1 mice. *Jpn J Cancer Res* 1987; **78:** 139–43.

4 Hirao K, Shinohara Y, Tsuda H, Fukushima S, Takahashi M, Ito N. Carcinogenic activity of quinoline on rat liver. *Cancer Res* 1976; **36:** 329–35.

5 Suzuki T, Wang X, Miyata Y, et al. Hepatocarcinogen quinoline induces G:C to C:G transversions in the cII gene in the liver of lambda/lacZ transgenic mice (MutaMouse). *Mutat Res* 2000; **456:** 73–81.

6 Rappaport SM, Yeowell-O'Connell K, Bodell W, Yager JW, Symaski E. An investigation of multiple biomarkers among workers exposed to styrene and styrene-7,8-oxide. *Cancer Res* 1996; **56:** 5410–16.

7 Kogevinas M, Ferro G, Andersen A, et al. Cancer mortality in a historical cohort study of workers exposed to styrene. *Scand J Work Environ Health* 1994; **20:** 251–61.

8 Coggon D, Ntani G, Harris EC, Palmer KT. Risk of cancer in workers exposed to styrene at eight British companies making glass reinforced plastics. *Occup Environ Med* 2015; **72:** 165–70.

9 Christensen MS, Vestergaard JM, d'Amore F, et al. Styrene exposure and risk of lymphohematopoietic malignancies in 73 036 reinforced plastics workers. *Epidemiology* 2018; **29:** 342–51.

10 Collins JJ, Bodner KM, Bus JS. Cancer mortality of workers exposed to styrene in the U.S. reinforced plastics and composite industry. *Epidemiology* 2013; **24:** 195–203.

11 Nissen MS, Stokholm ZA, Christensen MS, et al. Sinonasal adenocarcinoma following styrene exposure in the reinforced plastics industry. *Occup Environ Med* 2018; **0:** 1–3

12 Cruzan G, Bus JS, Banton MI, et al. Editor's highlight: complete attenuation of mouse lung cell proliferation and tumorigenicity in CYP2F2 knockout and CYP2F1 humanized mice exposed to inhaled styrene for up to 2 years supports a lack of human relevance. *Toxicol Sci* 2017; **159:** 413–21.

13 Cruzan G, Cushman JR, Andrews LS, et al. Chronic toxicity/oncogenicity study of styrene in CD-1 mice by inhalation exposure for 104 weeks. *J Appl Toxicol* 2001; **21:** 185–98.

14 Ponomarkov V, Tomatis L. Effects of long-term oral administration of styrene to mice and rats. *Scand J Work Environ Health* 1978; **4** (suppl 2)**:** 127–35.

15 Conti B, Maltoni C, Perino G, Ciliberti A. Long-term carcinogenicity bioassays on styrene administered by inhalation, ingestion and injection and styrene oxide administered by ingestion in Sprague-Dawley rats, and para-methylstyrene administered by ingestion in Sprague-Dawley rats and Swiss mice. *Ann N Y Acad Sci* 1988; **534:** 203–34.

16 Bastlová T, Vodicka P, Peterková K, Hemminki K, Lambert B. Styrene oxide-induced HPRT mutations, DNA adducts and DNA strand breaks in cultured human lymphocytes. *Carcinogenesis* 1995; **16:** 2357–62.

17 Cruzan G, Bus J, Hotchkiss J, Harkema J, Banton M, Sarag S. CYP2F2-generated metabolites, not styrene oxide, are a key event mediating the mode of action of styrene-induced mouse lung tumors. *Regul Toxicol Pharmacol* 2012; **62:** 214–20.

18 Lijinsky W. Rat and mouse forestomach tumors induced by chronic oral administration of styrene oxide. *J Natl Cancer Inst* 1986; **77:** 471–76.

19 Ponomarkov V, Cabral JRP, Wahrendorf J, et al. A carcinogenicity study of styrene-7,8-oxide in rats. *Cancer Lett* 1984; **24:** 95–101.

Bilag 2. Følgebreve, spørgeskema og kodebog

Styren og **Risiko** for **Kræft**
STRIKT

regionmidtjylland

Dato
November 2013

Arbejdsmedicinsk Klinik
Aarhus Universitetshospital
Nørrebrogade 44,
Bygn. 2C
8000 Aarhus C

Direkte tel.
7846 4278

Ref.
STRIKT1

Bidrag med din unikke viden og vind et gavekort på 500 kr.

Vi er i gang med en stor undersøgelse[1], hvor vi ser på om ansatte i den danske glasfiberindustri har forøget risiko for kræft. Vi har derfor brug for at vide mere om dit arbejde og dine ryge- og alkoholvaner. Vi håber derfor, du vil svare på 13 korte spørgsmål.

Når du har svaret på de 13 spørgsmål, lægges spørgeskemaet i den medfølgende svarkuvert og sendes med posten – *portoen er betalt*.

Når vi har modtaget dit udfyldte spørgeskema, deltager du automatisk i lodtrækningen om ét af 75 gavekort á 500 kr. til en af Coops butikker (Kvickly, SuperBrugsen eller Dagli'Brugsen). Vinderne udtrækkes umiddelbart efter afslutningen af undersøgelsen og får tilsendt gavekortet direkte med posten.

Undersøgelsen foretages med opbakning fra 3F og Plastindustrien. Vi vil naturligvis behandle dine oplysninger *100% fortroligt*, og resultaterne vil kun blive anvendt i *anonymiseret form*.

På forhånd mange tak for din hjælp!

Med venlig hilsen

Mette Skovgaard Christensen
Læge

Henrik A. Kolstad
Overlæge

1: Spørgeskemaundersøgelsen er en del af projektet "Erhvervsmæssig eksponering for styren og risiko for kræft: En 40 års opfølgningsundersøgelse blandt ansatte i den danske glasfiberplastindustri"
Oplysningerne fra spørgeskemaundersøgelsen vil blive koblet med registeroplysninger fra blandt andet Danmarks Statistik og Sundhedsstyrelsen. Det er frivilligt at deltage, og du kan til enhver tid tilbagekalde dit samtykke om deltagelse ved at kontakte Mette Skovgaard Christensen på mail metskoch@rm.dk eller på tlf. 7846 4278.
Projektet er godkendt af Datatilsynet og overholder reglerne i Persondataloven. Datatilsynet har fastsat nærmere vilkår for projektet til beskyttelse af de registreredes privatliv.
Projektet er finansieret med støtte fra Arbejdsmiljøforskningsfonden.

Århus Universitetshospital
ÅRHUS SYGEHUS

Bidrag med din viden om dit arbejde og hjælp os!

For 14 dage siden skrev vi til dig og spurgte, om du ville deltage i en spørgeskemaundersøgelse. Vi har desværre ikke hørt fra dig.
Vi er i gang med at undersøge om nuværende og tidligere ansatte i den danske glasfiberindustri har forøget risiko for kræft.[1]

Du får tilsendt dette brev, fordi du på et tidspunkt i perioden 1964-2009 har været ansat på en virksomhed, som *formodes* at producere glasfiber. Hvis du *ikke* mener, dette er tilfældet, bedes du blot svare "nej" i spørgsmål 1. Ellers håber vi, du vil bruge 5-10 minutter på at svare på de 13 korte spørgsmål.
I tilfælde af, at du har mistet spørgeskemaet+svarkuverten (udsendt i starten af november), vil du automatisk få tilsendt et nyt eksemplar i starten af december.

Når du har indsendt spørgeskemaet, deltager du automatisk i lodtrækningen om ét af 75 gavekort på 500 kr. til Coop (Kvickly, SuperBrugsen eller Dagli'Brugsen).
Der er opbakning til undersøgelsen fra 3F og Plastindustrien, og din besvarelse vil blive behandlet *fuldt fortroligt*. Resultatet af undersøgelsen vil kun blive anvendt i *anonymiseret form*.

Hvis du allerede har udfyldt og indsendt spørgeskemaet, beklager vi ulejligheden, og du bedes venligst se bort fra dette brev.

På forhånd mange tak for hjælpen!

Med venlig hilsen

Mette Skovgaard Christensen
Læge
tlf. 7846 4278
metskoch@rm.dk

Henrik Kolstad
Overlæge

Dato
November 2013

Arbejdsmedicinsk Klinik
Aarhus Universitetshospital
Nørrebrogade 44,
Bygn. 2C
8000 Aarhus C

Direkte tel.
7846 4278

Ref.
STRIKT2

1: Spørgeskemaundersøgelsen er en del af projektet "Erhvervsmæssig eksponering for styren og risiko for kræft: En 40 års opfølgningsundersøgelse blandt ansatte i den danske glasfiberplastindustri"
Oplysningerne fra spørgeskemaundersøgelsen vil blive koblet med registeroplysninger fra blandt andet Danmarks Statistik og Sundhedsstyrelsen. Det er frivilligt at deltage, og du kan til enhver tid tilbagekalde dit samtykke om deltagelse ved at kontakte Mette Skovgaard Christensen på mail metskoch@rm.dk eller på tlf. 7846 4278.
Projektet er godkendt af Datatilsynet og overholder reglerne i Persondataloven. Datatilsynet har fastsat nærmere vilkår for projektet til beskyttelse af de registreredes privatliv.
Projektet er finansieret med støtte fra Arbejdsmiljøforskningsfonden.

Sidste chance for at vinde et gavekort!

Indenfor den seneste måned har vi sendt dig to breve med opfordring til at svare på 13 korte spørgsmål[1]. Vi har desværre ikke hørt fra dig.

Hvorfor bliver jeg spurgt?

Du får tilsendt dette brev, fordi du på et tidspunkt i perioden 1964-2009 har været ansat på en virksomhed, som *formodes* at producere glasfiber. Oplysningerne stammer fra ATP-registeret (Arbejdsmarkedets Tillægspension). Hvis du dog *ikke* mener, dette er tilfældet, bedes du blot svare "nej" i spørgsmål 1 og sende spørgeskemaet retur i den medfølgende svarkuvert - *portoen er betalt*. Ellers håber vi, du vil svare på de 13 spørgsmål.

Når du har indsendt spørgeskemaet, deltager du automatisk i lodtrækningen om ét af 75 gavekort på 500 kr. til Coop. Vinderne får tilsendt gavekortet direkte med posten.
Der er opbakning til undersøgelsen fra 3F og Plastindustrien og din besvarelse vil blive behandlet *fuldt fortroligt*. Resultatet af undersøgelsen vil kun blive anvendt i *anonymiseret form*.

Hvis du allerede har udfyldt og indsendt spørgeskemaet, beklager vi ulejligheden, og du bedes venligst se bort fra dette brev. Der kan være op til 14 dages forsinkelse på registreringen.

Har du spørgsmål eller kommentarer til undersøgelsen, bedes du ringe på tlf. 7846 4278 (der er desværre en trykfejl i telefonnummeret på forsiden af spørgeskemaet!)

På forhånd mange tak for hjælpen!

Med venlig hilsen

Mette Skovgaard Christensen
Læge
7846 4278 / metskoch@rm.dk

Henrik A. Kolstad
Overlæge

Dato
December 2013

Arbejdsmedicinsk Klinik
Aarhus Universitetshospital
Nørrebrogade 44,
Bygn. 2C
8000 Aarhus C

Direkte tel.
7846 4278

Ref.
STRIKT3

1: Spørgeskemaundersøgelsen er en del af projektet "Erhvervsmæssig eksponering for styren og risiko for kræft: En 40 års opfølgningsundersøgelse blandt ansatte i den danske glasfiberplastindustri"
Oplysningerne fra spørgeskemaundersøgelsen vil blive koblet med registeroplysninger fra blandt andet Danmarks Statistik og Sundhedsstyrelsen. Det er frivilligt at deltage, og du kan til enhver tid tilbagekalde dit samtykke om deltagelse ved at kontakte Mette Skovgaard Christensen på mail metskoch@rm.dk eller på tlf. 7846 4278.
Projektet er godkendt af Datatilsynet og overholder reglerne i Persondataloven. Datatilsynet har fastsat nærmere vilkår for projektet til beskyttelse af de registreredes privatliv.
Projektet er finansieret med støtte fra Arbejdsmiljøforskningsfonden.

Styren og **Risiko** for **Kræft**
STRIKT

Navn Efternavn
Adresse husnummer
Postnummer BY

Tillykke du har vundet et gavekort!

Spørgeskemaundersøgelsen[1] blandt tidligere og nuværende ansatte i den danske glasfiberindustri er nu slut. Vi har derfor trukket lod om 75 gavekort til Coop blandt alle, som har deltaget. Du er en af de heldige, som har vundet. Der er vedlagt 2 gavechecks på hver kr. 250, som kan bruges i Coops butikker (SuperBrugsen, Kvickly, Dagli'Brugsen eller Fakta)[2]

Vi er stolte og beærede over den store opbakning og deltagelse i undersøgelsen. Ud af 15.000 mulige deltagere har godt 11.500 svaret enten ved at indsende skemaet, via mail eller telefonisk.
Vi glæder os til at bruge oplysningerne videre i vores projekt. Der vil efter planen blive offentliggjort resultater fra undersøgelsen sommer 2015.

Tusind tak for din deltagelse!

Med venlig hilsen

Mette Skovgaard Christensen
Læge

Henrik A. Kolstad
Overlæge

Dato
Januar 2014

Arbejdsmedicinsk Klinik
Aarhus Universitetshospital
Nørrebrogade 44,
Bygn. 2C
8000 Aarhus C

Direkte tel.
7846 4278

Ref.
STRIKT4

1: Spørgeskemaundersøgelsen er en del af projektet "Erhvervsmæssig eksponering for styren og risiko for kræft: En 40 års opfølgningsundersøgelse blandt ansatte i den danske glasfiberplastindustri"
Oplysningerne fra spørgeskemaundersøgelsen vil blive koblet med registeroplysninger fra blandt andet Danmarks Statistik og Sundhedsstyrelsen. Det er frivilligt at deltage, og du kan til enhver tid tilbagekalde dit samtykke om deltagelse ved at kontakte Mette Skovgaard Christensen på mail metskoch@rm.dk eller på tlf. 7846 4278.
Projektet er godkendt af Datatilsynet og overholder reglerne i Persondataloven. Datatilsynet har fastsat nærmere vilkår for projektet til beskyttelse af de registreredes privatliv.
Projektet er finansieret med støtte fra Arbejdsmiljøforskningsfonden.
2:Vi skal gøre opmærksom på at gevinster vundet i forbindelse med spørgeskemaundersøgelsen ifølge den danske skattelovgivning skal opgives på Selvangivelsen som B-indkomst.

Styren og **Risiko** for **Kræft**
STRIKT

Spørgeskema

2013

Spørgeskemaet består af 13 spørgsmål. Der er primært tale om afkrydsning, men vær opmærksom på, at du i spørgsmål 10-13 skal skrive tal i de tilhørende bokse.
Hvis du aldrig har arbejdet i en virksomhed, som har støbt glasfiber med brug af polyester/styren, skal du blot svare på spørgsmål 1.

Har du spørgsmål til spørgeskemaet eller undersøgelsen generelt, er du velkommen til at kontakte projektansvarlig, Mette Skovgaard Christensen, på mail metskoch@rm.dk eller telefon 7846 4218.

På forhånd tusind tak for din deltagelse!

Arbejdsmedicinsk Klinik
Aarhus Universitetshospital
Nørrebrogade 44, bygning 2C
8000 Aarhus
ATT. Mette Skovgaard Christensen
Tlf. 7846 4278

Århus Universitetshospital
ÅRHUS SYGEHUS

midt
regionmidtjylland

DANSK
ramazzini
CENTER
forskning i miljø
og arbejdsmedicin

AARHUS UNIVERSITET

1. Har du arbejdet i en virksomhed, som støbte glasfiber med polyester/styren?
(Sæt kun ét kryds)

Ja..... ☐ → Gå til spørgsmål 2
Nej..... ☐ → Spørgeskemaet er slut
Ved ikke..... ☐ → Gå til spørgsmål 9

2. Har du *selv* arbejdet med støbning af glasfiber med polyester/styren?
(Sæt kun ét kryds)

Ja..... ☐
Nej..... ☐ → Gå til spørgsmål 8

3. Hvornår har du arbejdet med støbning af glasfiber med polyester/styren?
(Sæt kryds, gerne flere)

Før 1960..... ☐
1960'erne..... ☐
1970'erne..... ☐
1980'erne..... ☐
1990'erne..... ☐
Efter år 2000..... ☐
Ved ikke..... ☐

4. Hvor længe har du arbejdet med støbning af glasfiber med polyester/styren?
(Sæt kun ét kryds)

Mindre end 1 år..... ☐
1-4 år..... ☐
5-9 år..... ☐
Mere end 10 år..... ☐
Ved ikke..... ☐

5. Hvor ofte arbejdede du i gennemsnit med støbning af glasfiber med polyester/styren?
(Sæt kun ét kryds)

- 5 dage eller mere om ugen..... ☐
- 2-4 dage om ugen..... ☐
- 1 dag om ugen..... ☐
- Sjældnere..... ☐
- Ved ikke..... ☐

6. Hvad var produktionsmetoden?
(Sæt kryds, gerne flere)

- Håndoplæg/laminering..... ☐
- Sprøjtning..... ☐
- Vakuumstøbning..... ☐
- Pultrudering..... ☐
- Presning (kold/varm)..... ☐
- Injektionssprøjtning..... ☐
- Andet..... ☐
- Ved ikke..... ☐

7. Anvendte du åndedrætsværn, mens du støbte glasfiber med polyester/styren?
(Sæt kun ét kryds)

- Ja, hele tiden..... ☐
- Ja, det meste af tiden..... ☐
- Ja, noget af tiden..... ☐
- Ja, lidt af tiden..... ☐
- Nej, på intet tidspunkt..... ☐
- Ved ikke..... ☐

8. Har du arbejdet i lokaler, hvor *andre* samtidig støbte glasfiber med polyester/styren?
(sæt kun ét kryds)

- Ja..... ☐
- Nej..... ☐
- Ved ikke..... ☐

9. Ryger du?
(sæt kun ét kryds)

Ja..... ☐
Nej, jeg er holdt op..... ☐
Nej, jeg har aldrig røget..... ☐ → Gå til spørgsmål 13

10. Hvis du ryger eller har røget: Hvor gammel var du, da du begyndte at ryge?
(skriv alder)

Alder..... ☐☐ år
Ved ikke*(sæt kryds)*..... ☐

11. Hvis du er holdt op med at ryge: Hvor gammel var du, da du stoppede?
(skriv alder)

Alder..... ☐☐ år
Ved ikke*(sæt kryds)*..... ☐

12. Hvor meget ryger du - eller røg du – i gennemsnit *om dagen*?
(skriv antal)

Cigaretter..... ☐☐ Stk
Cerutter/cigarer..... ☐☐ Stk
Pibestop..... ☐☐ Stk
Ved ikke*(sæt kryds)*..... ☐

13. Hvor mange genstande alkohol drak du i gennemsnit *om ugen*?
(skriv antal genstande. 1 genstand= 1 flaske øl eller 1 glas vin eller 2 cl. spiritus)

Da du var 20-29 år..... ☐☐ genstande
Da du var 30-39 år..... ☐☐ genstande
Da du var 40-49 år..... ☐☐ genstande
Da du var 50-59 år..... ☐☐ genstande
Da du var 60-69 år..... ☐☐ genstande
Ved ikke*(sæt kryds)*..... ☐

Tusind tak for din deltagelse!

Kodebog

Spørgeskema

2013

STRIKT-projektet

Arbejdsmedicinsk Klinik
Aarhus Universitetshospital
Nørrebrogade 44, bygning 2C
8000 Aarhus
ATT. Mette Skovgaard Christensen
Tlf. 7846 4278

Århus Universitetshospital
ÅRHUS SYGEHUS
midt regionmidtjylland
DANSK ramazzini CENTER forskning i miljø og arbejdsmedicin
AARHUS UNIVERSITET

1. Har du arbejdet i en virksomhed, som støbte glasfiber med polyester/styren?
(Sæt kun ét kryds)

Ja	**1**
Nej	**0**
Ved ikke	**8888**
Ubesvaret	**9999**

2. Har du *selv* arbejdet med støbning af glasfiber med polyester/styren?
(Sæt kun ét kryds)

Ja	**1**
Nej	**0**
Ubesvaret	**9999**

3. Hvornår har du arbejdet med støbning af glasfiber med polyester/styren?
(Sæt kryds, gerne flere)

Før 1960	**1**
1960'erne	**2**
1970'erne	**3**
1980'erne	**4**
1990'erne	**5**
Efter år 2000	**6**
Ved ikke	**8888**
Ubesvaret	**9999**

4. Hvor længe har du arbejdet med støbning af glasfiber med polyester/styren?
(Sæt kun ét kryds)

Mindre end 1 år	**1**
1-4 år	**2**
5-9 år	**3**
Mere end 10 år	**4**
Ved ikke	**8888**
Ubesvaret	**9999**

5. Hvor ofte arbejdede du i gennemsnit med støbning af glasfiber med polyester/styren?
(Sæt kun ét kryds)

5 dage eller mere om ugen..... **1**
2-4 dage om ugen..... **2**
1 dag om ugen..... **3**
Sjældnere..... **4**
Ved ikke..... **8888**
Ubesvaret..... **9999**

6. Hvad var produktionsmetoden?
(Sæt kryds, gerne flere)

Håndoplæg/laminering..... **1**
Sprøjtning..... **2**
Vakuumstøbning..... **3**
Pultrudering..... **4**
Presning (kold/varm)..... **5**
Injektionssprøjtning..... **6**
Andet..... **7**
Ved ikke..... **8888**
Ubesvaret..... **9999**

7. Anvendte du åndedrætsværn, mens du støbte glasfiber med polyester/styren?
(Sæt kun ét kryds)

Ja, hele tiden..... **1**
Ja, det meste af tiden..... **2**
Ja, noget af tiden..... **3**
Ja, lidt af tiden..... **4**
Nej, på intet tidspunkt..... **0**
Ved ikke..... **8888**
Ubesvaret..... **9999**

8. Har du arbejdet i lokaler, hvor *andre* samtidig støbte glasfiber med polyester/styren?
(sæt kun ét kryds)

Ja..... **1**
Nej..... **0**
Ved ikke..... **8888**
Ubesvaret..... **9999**

9. Ryger du?
(sæt kun ét kryds)

Ja..... **1**
Nej, jeg er holdt op..... **2**
Nej, jeg har aldrig røget..... **0**
Ubesvaret..... **9999**

10. Hvis du ryger eller har røget: Hvor gammel var du, da du begyndte at ryge?
(skriv alder)

Alder..... **ANGIVET TAL**
Ved ikke*(sæt kryds)*..... **8888**
Ubesvaret..... **9999**

11. Hvis du er holdt op med at ryge: Hvor gammel var du, da du stoppede?
(skriv alder)

Alder..... **ANGIVET TAL**
Ved ikke*(sæt kryds)*..... **8888**
Ubesvaret..... **9999**

12. Hvor meget ryger du - eller røg du – i gennemsnit *om dagen*?
(skriv antal)

Cigaretter..... **A- ANGIVET TAL**
Cerutter/cigarer..... **B-ANGIVET TAL**
Pibestop..... **C-ANGIVET TAL**
Ved ikke*(sæt kryds)*..... **8888**
Ubesvaret..... **9999**

13. Hvor mange genstande alkohol drak du i gennemsnit *om ugen*?
(skriv antal genstande. 1 genstand= 1 flaske øl eller 1 glas vin eller 2 cl. spiritus)

Da du var 20-29 år..... **A- ANGIVET TAL**
Da du var 30-39 år..... **B- ANGIVET TAL**
Da du var 40-49 år..... **C- ANGIVET TAL**
Da du var 50-59 år..... **D- ANGIVET TAL**
Da du var 60-69 år..... **E- ANGIVET TAL**
Ved ikke*(sæt kryds)*..... **8888**
Ubesvaret..... **9999**

Tusind tak for din deltagelse!

Bilag 3. Afslutningsskema til Arbejdsmiljøforskningsfonden