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Occupational exposure to nickel and hexavalent chromium and the risk of lung cancer in a pooled analysis of case-control studies (SYNERGY)

Thomas Behrens[1] | Calvin Ge[2] | Roel Vermeulen[2] | Benjamin Kendzia[1] | Ann Olsson[3] | Joachim Schüz[3] | Hans Kromhout[2] | Beate Pesch[1] | Susan Peters[2] | Lützen Portengen[2] | Per Gustavsson[4] | Dario Mirabelli[5] | Pascal Guénel[6] | Danièle Luce[7] | Dario Consonni[8] | Neil E. Caporaso[9] | Maria Teresa Landi[9] | John K. Field[10] | Stefan Karrasch[11,12] | Heinz-Erich Wichmann[11] | Jack Siemiatycki[13] | Marie-Elise Parent[14] | Lorenzo Richiardi[5] | Lorenzo Simonato[15] | Karl-Heinz Jöckel[16] | Wolfgang Ahrens[17] | Hermann Pohlabeln[17] | Guillermo Fernández-Tardón[18] | David Zaridze[19] | John R. McLaughlin[20] | Paul A. Demers[21] | Beata Świątkowska[22] | Jolanta Lissowska[23] | Tamás Pándics[24] | Eleonora Fabianova[25] | Dana Mates[26] | Vladimir Bencko[27] | Lenka Foretova[28] | Vladimír Janout[29] | Paolo Boffetta[30,31] | Bas Bueno-de-Mesquita[32†] | Francesco Forastiere[33] | Kurt Straif[34,35] | Thomas Brüning[1]

[1]Institute for Prevention and Occupational Medicine of the German Social Accident Insurance—Institute of the Ruhr-University Bochum (IPA), Germany

[2]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

[3]International Agency for Research on Cancer (IARC/WHO), Lyon, France

[4]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[5]Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin, Turin, Italy

[6]Center for Research in Epidemiology and Population Health (CESP), Team Exposome and Heredity, U1018 Inserm, University Paris-Saclay, Institut Gustave Roussy, Villejuif, France

[7]Univ. Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)—UMR_S 1085, Pointe-à-Pitre, France

[8]Epidemiology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[9]National Cancer Institute, Bethesda, Maryland, USA

[10]Roy Castle Lung Cancer Research Programme, Department of Molecular and Clinical Cancer Medicine, The University of Liverpool, Liverpool, UK

[11]Institute of Epidemiology, Helmholtz Zentrum München—German Research Center for Environmental Health, Neuherberg, Germany

[12]Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital LMU Munich; Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research (DZL), Munich, Germany

Abbreviations: CI, confidence interval; Cr(III), trivalent chromium; Cr(VI), hexavalent chromium; IARC, International Agency for Research on Cancer; LOD, limit of detection; OR, odds ratio; RERI, relative excess risk due to interaction; SCOEL, European Union Scientific Committee on Occupational Exposure Limits.

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[13]University of Montreal Hospital Research Center (CRCHUM), Montreal, Canada
[14]Epidemiology and Biostatistics Unit, Centre Armand-Frappier Santé Biotechnologie, Institut national de la recherche scientifique, Laval, Quebec, Canada
[15]Department of Cardiovascular Sciences and Public Health, University of Padova, Padova, Italy
[16]Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany
[17]Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany
[18]Health Research Institute of Asturias, University of Oviedo, ISPA and CIBERESP, Spain
[19]Department of Epidemiology and Prevention, N.N. Blokhin National Medical Research Centre of Oncology, Moscow, Russia
[20]Dalla Lana School of Public Health, University of Toronto, Toronto, Canada
[21]Occupational Cancer Research Centre, Ontario Health, Toronto, Canada
[22]The Nofer Institute of Occupational Medicine, Lodz, Poland
[23]Department of Cancer Epidemiology and Prevention, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[24]National Public Health Center, Budapest, Hungary
[25]Regional Authority of Public Health, Banska Bystrica, Slovakia
[26]National Institute of Public Health, Bucharest, Romania
[27]Institute of Hygiene and Epidemiology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic
[28]Masaryk Memorial Cancer Institute, Brno, Czech Republic
[29]Faculty of Health Sciences, Palacky University, Olomouc, Czech Republic
[30]Stony Brook Cancer Center, Stony Brook University, Stony Brook, New York, USA
[31]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[32]Centre for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
[33]Environmental Research Group, School of Public Health, Imperial College, London, UK, and National Research Council (CNR-Irib), Palermo, Italy
[34]ISGlobal, Barcelona, Spain
[35]Boston College, Chestnut Hill, Massachusetts, USA

Correspondence
Thomas Behrens, Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-University Bochum (IPA), Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany.
Email: thomas.behrens@dguv.de

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Abstract

There is limited evidence regarding the exposure-effect relationship between lung-cancer risk and hexavalent chromium (Cr(VI)) or nickel. We estimated lung-cancer risks in relation to quantitative indices of occupational exposure to Cr(VI) and nickel and their interaction with smoking habits. We pooled 14 case-control studies from Europe and Canada, including 16 901 lung-cancer cases and 20 965 control subjects. A measurement-based job-exposure-matrix estimated job-year-region specific exposure levels to Cr(VI) and nickel, which were linked to the subjects' occupational histories. Odds ratios (OR) and associated 95% confidence intervals (CI) were calculated by unconditional logistic regression, adjusting for study, age group, smoking habits and exposure to other occupational lung carcinogens. Due to their high correlation, we refrained from mutually adjusting for Cr(VI) and nickel independently. In men, ORs for the highest quartile of cumulative exposure to CR(VI) were 1.32 (95% CI 1.19-1.47) and 1.29 (95% CI 1.15-1.45) in relation to nickel. Analogous results among women were: 1.04 (95% CI 0.48-2.24) and 1.29 (95% CI 0.60-2.86), respectively. In men, excess lung-cancer risks due to occupational Cr(VI) and nickel exposure were also observed in each stratum of never, former and current smokers. Joint effects of Cr(VI) and nickel with smoking were in general greater than additive, but not different from multiplicative. In summary, relatively low cumulative levels of occupational exposure to Cr(VI) and nickel were associated with increased ORs for lung cancer, particularly in men. However, we cannot rule out a combined classical measurement and Berkson-type of error structure, which may cause differential bias of risk estimates.

KEYWORDS
metals, pulmonary cancer, smoking, SYNERGY, welders

What's new?

Occupational exposure to hexavalent chromium (Cr(VI)) and nickel is associated with increased lung-cancer risk. Little is known, however, about quantitative exposure-effect relationships between lung cancer and Cr(VI) or nickel. Here, quantitative exposure-effect relationships were investigated using secondary measurement data from different regions and time periods across a wide range of jobs, with adjustment for smoking habits. Lung-cancer risk was elevated even at low cumulative exposure levels to Cr(VI) or nickel, particularly in men and regardless of smoking habits. The findings warrant ongoing surveillance for carcinogenic risks of occupational metal exposure.

1 | INTRODUCTION

The hexavalent form of chromium (Cr(VI)) has been long recognized as human carcinogen.[1] Exposure mainly arises in hot metal processes, during the processing of stainless steel, during surface treatment by polishing, sanding and grinding, and, historically, during the manufacture of chromium pigment.[2,3] In previous analyses of the German MEGA measurement database, we observed the highest Cr(VI) concentrations in spray painting and hard-chromium plating, and also in welding fumes from shielded metal arc welding and flux-cored arc welding.[4] Determination of Cr(VI) is difficult as it is frequently deoxidized to the more stable trivalent chromium (Cr(III)).[5] In contrast to Cr(III), Cr(VI) readily passes cell membranes. Intracellular reduction to Cr(III) may lead to oxidative stress, resulting in protein and DNA damage, genomic instability, cytotoxicity, tissue damage, chronic inflammation and epigenetic changes such as microRNA, histone modification and DNA methylation which all may trigger carcinogenesis.[6] The European Union Scientific Committee on Occupational Exposure Limits (SCOEL) estimated an "acceptable" lifetime excess risk of four additional lung-cancer cases per 1000 after a 40-year occupational exposure to 1 μg/m^3 of Cr(VI) (40 μg/m^3-years).[7]

Nickel is a widespread occupational exposure in various jobs and industries, frequently with coexposure to chromium.[1] Exposure frequently occurs in nickel alloy and battery production.[8] It has been demonstrated that workers in several industrial processes (eg, metal-cutting and metal-forming activities, metal spraying, sintering, chemical production, manufacturing of glass, batteries and accumulators, as well as certain welding processes) have experienced exposures at median nickel concentrations above 10 μg/m^3, which is the recommended SCOEL threshold limit value to protect workers from carcinogenicity.[9,10] As early as 1979, working in nickel refineries was classified as Group 1 carcinogen by the International Agency for Research on Cancer (IARC),[11] and the same classification was later also assigned to various nickel compounds.[1]

So far, epidemiological evidence on the exposure-effect relationship between occupational exposure to Cr(VI) or nickel with lung-cancer risk primarily has been obtained from studies among workers in chromate production and in nickel refining.[12-14] Increased lung-cancer risks were also described in chromate pigment production and among chrome plating workers.[2]

At-risk occupations with exposures to Cr(VI) and nickel comprise welders as the largest workforce. Welding fumes have been classified as a Group 1 carcinogen,[15] and several job title-based analyses have demonstrated increased risks for lung cancer among professional,[16-18] but also occasional welders.[18] Due to the complex composition of welding fumes, it is challenging to attribute lung-cancer risk to one of its major components, which may be illustrated by the inability of many studies to demonstrate consistently elevated lung-cancer risks to Cr(VI) or nickel exposure in association with welding activities.[16,17]

There is little evidence showing quantitative, measurement-based exposure-effect relationships between Cr(VI) or nickel and lung cancer across a wide array of job activities, while adjusting for smoking habits. We therefore took advantage of data from the pooled SYNERGY case-control study of occupational lung cancer to estimate relative risks related to occupational exposure to Cr(VI) or nickel. The objectives of this paper were: (1) to estimate lung-cancer risk associated with quantitative indices of occupational exposure to Cr(VI) and to nickel; (2) to assess the shape of the exposure-effect relationship between each metal and lung cancer separately; and (3) to assess their joint effects with smoking habits.

2 | METHODS

2.1 | SYNERGY project

The detailed objectives, methods and aims of SYNERGY are described elsewhere.[19,20] Briefly, SYNERGY was established as an international pooled case-control study to investigate joint effects of occupational carcinogens (asbestos,[19] respirable crystalline silica,[20] polycyclic aromatic hydrocarbons,[21] chromium, nickel) and smoking[22] in the development of lung cancer. Over the years, our study has developed into an international platform for research on occupational lung cancer with 16 case-control studies from 22 study centers. For this analysis, we used data from the 14 original SYNERGY studies from Europe and Canada (Table S1), including 16 901 lung-cancer cases and 20 965 control subjects. More information about SYNERGY is available at http://synergy.iarc.fr.

2.2 | Assessment of occupational exposure to Cr(VI) and nickel

The development of the quantitative job-exposure matrix SYN-JEM to assess occupational exposure to Cr(VI) and nickel followed a protocol which has been described in detail elsewhere.[23] Briefly, personal measurements of chromium (n = 24 150) and nickel (n = 22 081), covering a period from the 1970s to 2009, were collected in the participating countries, compiled in the ExpoSYN database, and tagged with an ISCO-68 job title. Overall, 35% of the chromium and 28% of the nickel measurements were below the limit of detection (LOD).[23] We substituted these measurements with a random figure between 0 and the LOD, assuming that they followed the same log-normal probability distribution as the measurements above LOD.[24]

A standard linear mixed-effects model was developed to assign region- and time-specific exposure levels for each ISCO-68-based job title that was solicited from the subjects' self-reported job histories. Region/country and job title were used as random effects, whereas year of measurement, sampling duration, and a prior exposure rating from a semi-quantitative expert-based job-exposure matrix (DOMJEM) assigning no, low or high exposure levels[25] were included as fixed effects. The DOMJEM rating was used as an override for nonroutine measurements to set jobs considered to be nonexposed to 0 $\mu g/m^3$. In addition, models for Cr(VI) and nickel included the analytical method as fixed effect. Measurements conducted for jobs that were assumed by SYN-JEM to be nonexposed were retained in the model for the overall assessment of time trends and regional differences in Cr(VI) and nickel levels. Model-based estimates were used to calculate the amount of Cr(VI) based on specific Cr(VI) (n = 8363) and total chromium measurements (n = 15 787). For total chromium values a conversion factor set at a total chromium:Cr(VI) ratio of 3:1 was applied.[23]

The model yielded a linear temporal trend with an annual decrease of Cr(VI) concentrations of −2.7% and −1.2% per year for nickel. When there were <5 measurements for a specific job, the mean estimate of all jobs within the same unit or major group was used to base a job-specific exposure estimate on information from similar jobs.[23]

It should be noted that assigning quantitative exposure data as part of a job-exposure matrix may lead to a combined classical measurement and Berkson-type of error structure, which may cause over- or underestimation of coefficients in logistic-regression analysis.[26]

Lifetime cumulative exposure to Cr(VI) or nickel was calculated as the sum of the country/region-specific SYN-JEM estimates for each job and year. Cumulative indices were categorized according to quartiles based on the distribution among all (both sexes combined) control subjects. For interaction analyses a cutoff at the median was applied to define low and high exposure categories.

2.3 | Statistical analysis

We calculated odds ratios (OR) with 95% confidence intervals (CI) by unconditional logistic regression analysis. The main models included either Cr(VI) or nickel as the exposure variable, in addition to a number of covariates. Mutual adjustment was not performed in the main models, because a strong correlation between cumulative Cr(VI) and nickel levels was observed in subjects with coexposure to both metals (Pearson r = 0.75; 95% CI 0.74-0.76). The reference category therefore consisted of subjects who were not exposed occupationally to either Cr(VI) or to nickel.

To control for confounding, we employed two different models: OR1 was adjusted for study and age group (<45, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75+ years) and OR2 was additionally adjusted for cumulative cigarette consumption (log(cigarette pack-years+1)), smoking status including time-since-quitting smoking cigarettes (current smokers, stopping smoking 2-7 years, 8-15 years, 16-25, 26+ years before interview/diagnosis, never smokers), and ever employment in a "list A" job (yes/no). List A includes occupations and industries with an established lung cancer risk.[27,28] This approach is consistent with the other analyses in SYNERGY.[19-21]

Cigarette pack-years were calculated as smoking duration (years) x average cigarette smoking intensity per day/20. Current smokers included smokers who had stopped smoking within the last 2 years before the interview/diagnosis. Never smokers were defined as lifelong nonsmokers and subjects with a smoking history of <1 pack-year.

To visualize the functional form of the adjusted exposure-effect relationship between each agent (Cr(VI) or nickel) and lung-cancer risk for the fully adjusted model (OR2), we estimated restricted cubic spline functions and associated 95% CI. The optimal smoothing parameter was selected based on generalized cross-validation and under the assumption that the total number of degrees of freedom required for a biologically plausible model would not exceed three. Restricted cubic spline analyses also included lagged analyses, neglecting exposures that occurred 5, 10, 15 or 20 years before diagnosis (cases) or the interview (control subjects).

We assessed the additive interaction between smoking and Cr(VI) and nickel by estimating the "relative excess risk due to interaction" (RERI).[29] Possible departure from a multiplicative joint effect was assessed by testing a multiplicative interaction term in the statistical model.

We conducted several subgroup and sensitivity analyses to assess the robustness of our results: (a) We stratified analyses by hospital-based and population-based studies and study region (Northern Europe (Germany, Sweden, France, UK, The Netherlands); Southern Europe (Italy, Spain); East Europe (Czech Republic, Hungary, Poland, Romania, Russia, Slovakia); and Canada). (b) We restricted the study base to blue-collar workers to rule out a general blue-collar worker effect (ie, an increased risk associated with multiple hazardous exposures in blue-collar job activities). (c) We excluded welders and (d) we restricted analyses to workers who started working in 1960 as well as 1970 or later, because exposure data were scarce before the 1970s. (e) Although the main analyses contained only one of the two

TABLE 1 Descriptive characteristics of the study participants (16 901 lung-cancer cases, 20 965 control subjects) by exposure to hexavalent chromium (Cr(VI)) and nickel

		Exposed to Ni or Cr(VI)				Unexposed to Ni and Cr(VI)			
		Cases		Controls		Cases		Controls	
Characteristic	Exposure category	No. (%)	Median (IQR)	No. (%)	Median (IQR)	No. (%)	Median (IQR)	No. (%)	Median (IQR)
Men		4135		3823		9470		12 628	
Age [y]	Median (IQR)		63 (13)		63 (13)		64 (12)		63 (13)
	<45	132 (3)		177 (5)		354 (4)		718 (6)	
	45-65	2260 (55)		1955 (51)		4725 (50)		6227 (49)	
	65+	1743 (42)		1691 (44)		4391 (46)		5683 (45)	
Smoking status	Never smoker	116 (3)		846 (22)		374 (4)		3591 (28)	
	Former smoker	1397 (34)		1789 (47)		3390 (36)		5539 (44	
	Current smoker	2622 (63)		1188 (31)		5706 (60)		3498 (28)	
Cigarette pack-years (current and former smokers)	<10	202 (5)		594 (20)		490 (5)		2130 (24)	
	10 to <20	411 (10)		586 (20)		837 (9)		1746 (19)	
	20 to <40	1533 (39)		1067 (36)		3336 (37)		3004 (33)	
	40+	1873 (47)		730 (24)		4433 (49)		2157 (24)	
Years-since-quitting smoking (former smokers)	>2-7	521 (37)		306 (17)		1225 (36)		912 (16)	
	8-15	394 (28)		429 (24)		961 (28)		1262 (23)	
	16-25	297 (21)		516 (29)		747 (22)		1579 (29)	
	>25	185 (13)		538 (30)		457 (13)		1786 (32)	
Employed in "list A" job	Ever	922 (22)		668 (17)		807 (9)		656 (5)	
Lung-cancer cell type	Adenocarcinoma	896 (22)				2429 (26)			
	Squamous cell carcinoma	1885 (46)				3943 (42)			
	Small-cell lung cancer	703 (17)				1497 (16)			
	Other/unspecified	625 (15)				1548 (16)			
	Not available	26 (1)				53 (1)			
Nickel [μg/m^3-y]			22.7 (64)		21.5 (60)				
Cr(VI) [μg/m^3-y]			42.8 (91)		40.8 (86)				
Women		161		146		3135		4368	
Age [y]	Median (IQR)		63 (14)		62 (15)		61 (16)		61 (17)
	<45	11 (7)		5 (3)		218 (7)		471 (11)	
	45-64	82 (51)		75 (51)		1696 (54)		2097 (48)	
	65+	68 (42)		66 (45)		1221 (39)		1800 (41)	
Smoking status	Never smoker	35 (22)		76 (52)		844 (27)		2640 (60)	
	Former smoker	24 (15)		35 (24)		621 (20)		857 (20)	
	Current smoker	102 (63)		35 (24)		1670 (53)		871 (20)	
Cigarette pack-years (current and former smokers)	<10	9 (7)		20 (29)		222 (10)		629 (36)	
	10-19	19 (15)		17 (24)		377 (16)		403 (23)	
	20 to <40	53 (42)		25 (36)		906 (40)		464 (27)	
	40+	45 (36)		8 (11)		786 (34)		232 (13)	
Years-since-quitting smoking (former smokers)	2-7 y	9 (38)		7 (20)		271 (44)		197 (23)	
	8-15 y	6 (25)		5 (14)		170 (27)		202 (24)	
	16-25 y	6 (25)		13 (37)		121 (19)		238 (28)	

(Continues)

TABLE 1 (Continued)

		Exposed to Ni or Cr(VI)				Unexposed to Ni and Cr(VI)			
		Cases		Controls		Cases		Controls	
Characteristic	Exposure category	No. (%)	Median (IQR)	No. (%)	Median (IQR)	No. (%)	Median (IQR)	No. (%)	Median (IQR)
	26+ y	3 (12)		10 (29)		59 (10)		220 (26)	
Employed in "list A" job	Ever	17 (11)		16 (11)		41 (1)		24 (1)	
Lung-cancer cell type	Not available	1 (1)				14 (1)			
	Adenocarcinoma	56 (35)				1371 (44)			
	Squamous cell carcinoma	37 (23)				638 (20)			
	Small-cell lung cancer	37 (23)				493 (16)			
	Other/unspecified	30 (19)				619 (20)			
Nickel [μg/m^3-y]	Median (IQR)		16.7 (30)		14.2 (29)				
Cr(VI) [μg/m^3-y]	Median (IQR)		26.2 (46)		26.0 (46)				

Abbreviations: Cr(VI), hexavalent chromium; IQR, interquartile range.

exposure variables of interest, we conducted a set of sensitivity analyses that included both Cr(VI) and nickel.

Statistical analyses were carried out using R statistical software (version 3.6.1).

3 | RESULTS

Among men, lifetime prevalence of exposure to Cr(VI) was 30% among cases and 23% among controls. Exposure prevalence to nickel was 24% (cases) and 19% (controls), of whom 77.7% of cases and 83% of controls were also exposed to Cr(VI). As expected, exposure prevalence was much lower among women than men (5% to Cr(VI) in both cases and controls). The exposure prevalence to nickel in females was 3% among both cases and controls (Table 2).

Differences in median cumulative exposure levels to Cr(VI) and nickel were less pronounced. The median Cr(VI) exposure in men was: 42.8 μg/m^3-years (cases) and 40.8 μg/m^3-years (controls) and in women 26.2 μg/m^3-years (cases) and 26 μg/m^3-years (controls). Median nickel exposure among men was 22.7 μg/m^3-years among cases and 21.5 μg/m^3-years among controls. Women showed 16.7 μg/m^3-years (cases) and 14.2 μg/m^3-years (controls), respectively (Table 1).

We observed similarly increased lung-cancer ORs for ever exposure to Cr(VI) and nickel among both sexes. Assessment of cumulative exposure revealed a close to monotonic exposure-effect trend among men in the fully adjusted model (ORs for the highest exposure category: Cr(VI): >99.5 μg/m^3-years; OR = 1.32, 95% CI 1.19-1.47 and nickel: >78.1 μg/m^3-years, OR = 1.29; 95% CI 1.15-1.45) (Table 2). For women, the exposure-effect relationships were less consistent with OR = 1.04; 95% CI 0.48-2.24 in the highest Cr(VI) category and OR = 1.29; 95% CI 0.60-2.86 in the highest nickel-exposure category (Table 2).

In men, we also observed a monotonic trend toward higher risk estimates with increasing duration of exposure to Cr(VI). Exposure for 30 years and more, compared to never exposed, showed increased ORs in the fully adjusted model (OR = 1.37; 95% CI 1.23-1.51 for Cr(VI) and OR = 1.23; 95% CI 1.09-1.38 for nickel). Risks peaked 10-19 years after cessation of exposure to Cr(VI) or nickel and then continuously declined toward baseline risk. The findings for women were less consistent (Table 2).

Subgroup analyses among males revealed more cases and slightly higher ORs in population-based studies than hospital-based studies (Tables 3 and 4). Compared to the full model, restricting the study base to male blue-collar workers and workers who started their job after 1960 showed a weaker exposure-effect relationship for Cr(VI) and nickel, although the highest exposure category still resulted in significantly increased ORs for lung cancer. Analyses restricted to workers starting after 1970 showed similar risk patterns, albeit less strong. Subgroup analyses among female subjects were based on few cases only, and the results were quite imprecise (Tables S3a and S3b). Lagging exposure by 5, 10, 15 and 20 years generated similar results (Table S4) compared to the unlagged risk estimates.

Center-specific results revealed some heterogeneity between study regions where results from Southern Europe matched those from the North European region showing increased ORs, whereas the picture was less homogeneous and the number of cases smaller in the other geographically similar study centers (see Tables S2a and S2b and Figures S1a and S1b).

Analyses using cubic splines showed a nearly linear exposure-effect relationship for nickel among males. The exposure-effect for

TABLE 2 Lung cancer odds ratios (OR) and 95% CI in relation to indices of occupational exposure to nickel and hexavalent chromium in the SYNERGY study

		Men							Women						
Indices of occupational exposure	Exposure category	Cases	Controls	OR1	95% CI	OR2	95% CI	99.4% CI[a]	Cases	Controls	OR1	95% CI	OR2	95% CI	99.4% CI[a]
Nickel	Never	10 389	13 311	1.0	Ref.	1.0	Ref.	Ref.	3145	4383	1.0	Ref.	1.0	Ref.	Ref.
	Ever	3216	3140	1.27	1.20-1.35	1.12	1.05-1.20	1.02-1.23	151	131	1.64	1.28-2.10	1.23	0.93-1.63	0.83-1.83
Duration (y)	1-9	1273	1375	1.13	1.04-1.23	1.01	0.92-1.11	0.88-1.15	102	79	1.84	1.36-2.50	1.36	0.96-1.91	0.84-2.20
	10-19	609	575	1.35	1.20-1.52	1.15	1.00-1.31	0.95-1.39	30	36	1.25	0.76-2.06	0.95	0.54-1.66	0.43-2.11
	20-29	487	419	1.47	1.29-1.68	1.26	1.08-1.46	1.01-1.56	13	8	2.02	0.84-5.15	1.53	0.58-4.32	0.38-6.26
	30+	847	771	1.37	1.23-1.51	1.23	1.09-1.38	1.04-1.44	6	8	1.03	0.33-2.99	0.87	0.25-2.85	0.16-4.74
Test for trend, *P*-value					<.001		<.001					.05		.59	
Excl. never exposed					<0.001		0.001					0.51		0.87	
Cr(VI)	Never	9474	12 631	1.0	Ref.	1.0	Ref.	Ref.	3137	4368	1.0	Ref.	1.0	Ref.	Ref.
	Ever	4131	3820	1.38	1.31-1.46	1.21	1.14-1.28	1.11-1.31	159	146	1.52	1.20-1.92	1.14	0.87-1.49	0.78-1.67
Duration (y)	1-9	1518	1628	1.17	1.09-1.27	1.04	0.95-1.13	0.92-1.18	110	90	1.69	1.27-2.26	1.28	0.93-1.77	0.81-2.03
	10-19	780	672	1.52	1.36-1.69	1.27	1.13-1.44	1.07-1.51	30	38	1.17	0.71-1.91	0.86	0.49-1.49	0.39-1.89
	20-29	647	531	1.60	1.42-1.80	1.34	1.17-1.53	1.10-1.62	13	9	1.77	0.76-4.34	1.24	0.48-3.34	0.32-4.81
	30+	1186	989	1.53	1.40-1.67	1.37	1.23-1.51	1.18-1.58	6	9	0.89	0.30-2.51	0.75	0.22-2.35	0.14-3.88
Test for trend, *P*-value					<.001		<.001					.12		.99	
Excl. never exposed					<0.001		<0.001					0.58		0.79	
Ni or Cr(VI)	Never	9470	12 628	1.0	Ref.	1.0	Ref.	Ref.	3135	4368	1.0	Ref.	1.0	Ref.	Ref.
	Ever	4135	3823	1.39	1.31-1.46	1.21	1.14-1.28	1.11-1.31	161	146	1.54	1.22-1.95	1.15	0.88-1.51	0.79-1.68
Ni and Cr(VI)	Never	10 393	13 314	1.0	Ref.	1.0	Ref.	Ref.	3147	4383	1.0	Ref.	1.0	Ref.	Ref.
	Ever	3212	3173	1.27	1.20-1.35	1.12	1.05-1.20	1.02-1.23	149	131	1.62	1.23-2.07	1.22	0.92-1.61	0.82-1.81
Cumulative exposure to nickel [μg/m^3-y]	>0 to ≤11.9	672	771	1.04	0.93-1.16	0.92	0.81-1.04	0.77-1.09	54	47	1.70	1.14-2.56	1.29	0.82-2.05	0.68-2.47
	>11.9 to ≤30.9	749	775	1.18	1.06-1.31	1.06	0.94-1.20	0.89-1.26	47	42	1.61	1.05-2.48	1.34	0.83-2.16	0.68-2.63
	>30.9 to ≤78.1	914	790	1.44	1.30-1.59	1.20	1.07-1.35	1.02-1.41	29	28	1.45	0.85-2.48	0.97	0.53-1.76	0.41-2.25
	>78.1	881	804	1.42	1.29-1.57	1.29	1.15-1.45	1.10-1.52	21	14	1.91	0.97-3.90	1.29	0.60-2.86	0.43-3.87
Test for trend, *P*-value					<.001		<.001					.06		.70	
Excl. never exposed					0.003		0.013					0.47		0.75	

(Continues)

TABLE 2 (Continued)

Indices of occupational exposure	Exposure category	Men							Women						
		Cases	Controls	OR1	95% CI	OR2	95% CI	99.4% CI[a]	Cases	Controls	OR1	95% CI	OR2	95% CI	99.4% CI[a]
Time since last nickel exposure (y)[b]	1-4	593	573	1.30	1.05-1.61	1.19	0.93-1.50	0.85-1.66	14	12	2.22	0.84-6.03	2.00	0.64-6.48	0.39-10.3
	5-9	374	319	1.48	1.18-1.84	1.23	0.96-1.58	0.86-1.75	10	9	2.27	0.76-6.92	1.41	0.42-4.76	0.26-7.73
	10-19	603	526	1.42	1.18-1.70	1.24	1.01-1.52	0.93-1.65	18	21	1.39	0.64-3.04	1.13	0.47-2.67	0.33-3.80
	20-29	493	486	1.27	1.09-1.47	1.06	0.89-1.25	0.83-1.34	33	27	1.88	1.03-3.46	1.61	0.83-3.15	0.63-4.11
	30-39	554	595	1.12	0.99-1.27	0.99	0.85-1.14	0.80-1.21	25	29	1.36	0.76-2.43	0.97	0.50-1.89	0.38-2.48
	40+	599	641	1.09	0.97-1.23	0.97	0.85-1.12	0.80-1.18	51	33	2.55	1.59-4.16	1.61	0.94-2.78	0.75-3.46
Test for trend, *P*-value					.02		.03					.08		.21	
Cumulative exposure to Cr(VI) [μg/m³-y]	>0 to ≤15.3	965	943	1.27	1.15-1.40	1.12	1.01-1.25	0.96-1.31	56	49	1.62	1.10-2.42	1.18	0.76-1.85	0.63-2.22
	>15.3 to ≤40.3	1028	950	1.38	1.26-1.52	1.19	1.07-1.32	1.03-1.38	46	41	1.50	0.97-2.31	1.24	0.76-2.03	0.62-2.48
	>40.3 to ≤99.5	1017	953	1.37	1.25-1.51	1.19	1.07-1.32	1.02-1.38	40	38	1.52	0.96-2.41	1.03	0.62-1.72	0.51-2.11
	>99.5	1121	974	1.51	1.37-1.65	1.32	1.19-1.47	1.14-1.53	17	18	1.27	0.64-2.51	1.04	0.48-2.24	0.35-3.06
Test for trend, *P*-value					<.001		<.001					.18		.89	
Excl. never exposed					0.01		0.07					0.82		0.83	
Time since last Cr(VI) exposure (y)[b]	1-4	836	720	1.50	1.24-1.81	1.28	1.04-1.59	0.95-1.73	16	14	2.01	0.83-4.99	1.54	0.55-4.45	0.35-6.67
	5-9	482	400	1.56	1.28-1.90	1.26	1.01-1.58	0.92-1.73	11	10	2.17	0.78-6.13	1.34	0.43-4.18	0.27-6.60
	10-19	781	651	1.51	1.28-1.78	1.28	1.07-1.54	0.99-1.66	17	24	1.13	0.52-2.43	0.86	0.36-2.01	0.26-2.87
	20-29	622	581	1.37	1.20-1.57	1.14	0.98-1.32	0.92-1.41	34	28	1.82	1.02-3.30	1.54	0.81-2.95	0.62-3.83
	30-39	703	695	1.25	1.11-1.40	1.06	0.93-1.21	0.88-1.28	25	30	1.30	0.72-2.29	0.91	0.47-1.76	0.36-2.32
	40+	707	773	1.09	0.98-1.22	0.98	0.86-1.11	0.82-1.17	56	40	2.18	1.40-3.43	1.50	0.91-2.48	0.74-3.04
Test for trend, *P*-value					<.001		.01					.05		.10	

Note: OR1 is adjusted for study and age group. OR2 is adjusted for study, age group, smoking (log(cigarette pack-years+1), time-since-quitting smoking (current smokers, stopping smoking 2-7 y, 8-15 y, 16-25, 26+ y before interview/diagnosis, never smokers)) and list A jobs.

[a]99.4% CI Bonferroni-corrected for nine subtests.

[b]OR2 in "time since last exposure" is in addition adjusted for duration (continuous) of exposure.

TABLE 3 Lung cancer odds ratios (OR) and 95% CI in relation to cumulative exposure to hexavalent chromium in subgroups of men in the SYNERGY study

Cumulative exposure [µg/m³-y]	Population-based studies				Hospital-based studies				Blue-collar workers only			
	Cases/Controls	OR2	95% CI	99.4% CI[a]	Cases/Controls	OR2	95% CI	99.4% CI[a]	Cases/Controls	OR2	95% CI	99.4% CI[a]
Unexposed	6916/9815	1.0	Ref.	Ref.	2478/2685	1.0	Ref.	Ref.	6773/7518	1.0	Ref.	Ref.
>0 to ≤15.3	740/707	1.17	1.03-1.32	0.97-1.36	150/139	1.09	0.83-1.42	0.74-1.49	963/938	1.02	0.92-1.14	0.87-1.20
>15.3 to ≤40.3	774/685	1.29	1.14-1.46	1.07-1.50	202/205	0.97	0.77-1.21	0.72-1.33	1028/945	1.08	0.97-1.20	0.93-1.26
>40.3 to ≤99.5	724/671	1.27	1.12-1.44	1.05-1.49	263/223	1.06	0.86-1.31	0.78-1.37	1016/947	1.09	0.97-1.21	0.93-1.26
>99.5	775/700	1.36	1.20-1.54	1.18-1.70	378/308	1.16	0.97-1.39	0.91-1.50	1117/965	1.21	1.09-1.35	1.04-1.41
Test for trend, *P*-value			<.001				.32				.01	
Excl. never exposed			0.15				0.59				0.07	
Cumulative exposure [µg/m³-y]	**Restricted to workers starting jobs 1960 or later**				**Restricted to workers starting jobs 1970 or later**				**Excluding regular welders**			
	Cases/Controls	**OR2**	**95% CI**	**99.4% CI[a]**	**Cases/Controls**	**OR2**	**95% CI**	**99.4% CI[a]**	**Cases/Controls**	**OR2**	**95% CI**	**99.4% CI[a]**
Unexposed	2379/3651	1.0	Ref.	Ref.	758/1539	1.0	Ref.	Ref.	9474/12631	1.0	Ref.	Ref.
>0 to ≤15.3	198/216	1.08	0.86-1.37	0.78-1.51	56/77	1.11	0.74-1.68	0.62-2.00	936/921	1.10	0.99-1.22	0.95-1.30
>15.3 to ≤40.3	224/234	1.26	1.01-1.58	0.92-1.74	67/90	1.31	0.89-1.92	0.76-2.24	954/883	1.18	1.06-1.31	1.02-1.39
>40.3 to ≤99.5	186/223	1.04	0.82-1.32	0.74-1.45	48/83	0.86	0.57-1.31	0.48-1.56	879/846	1.18	1.05-1.31	1.00-1.37
>99.5	212/207	1.30	1.03-1.64	0.93-1.81	36/42	1.28	0.76-2.17	0.61-2.69	843/785	1.25	1.12-1.40	1.07-1.48
Test for trend, *P*-value			.03				.79		<.001			
Excl. never exposed			0.30				0.35		0.07			

Note: OR2 is adjusted for study, age group, smoking (log(cigarette pack-years+1), time-since-quitting smoking (current smokers, stopping smoking 2-7, 8-15, 16-25, 26+ y before interview/diagnosis, never smokers)) and list A jobs.

[a]99.4% CI Bonferroni-corrected for nine subtests.

TABLE 4 Lung cancer odds ratios (OR) and 95% CI in relation to cumulative exposure to nickel in subgroups of men in the SYNERGY study

	Population-based studies				Hospital-based studies				Blue-collar workers only			
Cumulative exposure [μg/m³-y]	Cases/Controls	OR2	95% CI	99.4% CI[a]	Cases/Controls	OR2	95% CI	99.4% CI[a]	Cases/Controls	OR2	95% CI	99.4% CI[a]
Unexposed	7669/10 359	1.0	Ref.	Ref.	2657/2834	1.0	Ref.	Ref.	7685/8195	1.0	Ref.	Ref.
>0 to ≤11.9	431/484	0.94	0.81-1.10	0.78-1.16	138/149	0.87	0.67-1.14	0.59-1.19	672/769	0.84	0.75-0.96	0.71-1.01
>11.9 to ≤30.9	526/525	1.14	0.98-1.32	0.92-1.36	174/177	0.92	0.72-1.17	0.67-1.28	749/770	0.97	0.86-1.09	0.82-1.15
>30.9 to ≤78.1	650/583	1.20	1.05-1.37	1.01-1.47	240/189	1.17	0.94-1.46	0.86-1.57	912/785	1.10	0.98-1.23	0.93-1.29
>78.1	653/627	1.29	1.13-1.48	1.06-1.56	262/211	1.22	0.99-1.51	0.98-1.76	879/794	1.18	1.05-1.33	1.00-1.39
Test for trend, *P*-value			.004				.06				.03	
Excl. never exposed			0.12				0.03				0.01	

	Restricted to workers starting jobs 1960 or later				Restricted to workers starting jobs 1970 or later				Excluding regular welders			
Cumulative exposure [μg/m³-y]	Cases/Controls	OR2	95% CI	99.4% CI[a]	Cases/Controls	OR2	95% CI	99.4% CI[a]	Cases/Controls	OR2	95% CI	99.4% CI[a]
Unexposed	2563/3782	1.0	Ref.	Ref.	810/1586	1.0	Ref.	Ref.	10 389/13 311	1.0	Ref.	Ref.
>0 to ≤11.9	125/172	0.85	0.65-1.13	0.58-1.26	36/54	0.98	0.60-1.61	0.48-1.98	590/698	0.86	0.76-0.98	0.74-1.06
>11.9 to ≤30.9	162/184	1.11	0.86-1.43	0.77-1.59	46/60	1.34	0.83-2.12	0.70-2.57	643/678	1.06	0.93-1.20	0.89-1.28
>30.9 to ≤8.1	171/224	0.95	0.74-1.20	0.67-1.33	39/83	0.73	0.47-1.14	0.39-1.37	741/674	1.56	1.03-1.31	0.98-1.38
>78.1	178/169	1.42	1.10-1.84	0.98-2.05	34/48	1.15	0.69-1.93	0.55-2.40	723/705	1.22	1.08-1.37	1.02-1.44
Test for trend, *P*-value		.11				.63			.001			
Excl. never exposed		0.00				0.69			0.004			

Note: OR2 is adjusted for study, age group, smoking (log(cigarette pack-years+1), time-since-quitting smoking (current smokers, stopping smoking 2-7, 8-15, 16-25, 26+ y before interview/diagnosis, never smokers)) and list A jobs.

[a]99.4% CI Bonferroni-corrected for nine subtests.

Cr(VI) among males and among female subjects for both metals were linear (Figure 1).

When we stratified the analyses by smoking status, we observed similarly increased ORs for Cr(VI) exposure above the median (40.23 μg/m^3-years) among current smokers, former smokers, and never smokers (Tables S5-S7). In men, ORs were strongest for squamous-cell and small-cell lung cancer subtypes, whereas there was no consistent association between Cr(VI) exposure and adenocarcinoma. Risk estimates in never smokers appeared to be strongest for small-cell cancer of the lung (Table S5). Similar patterns were observed for occupational nickel exposure above the median of 30.75 μg/m^3-years (Table S6).

Among men, the joint effect of smoking and Cr(VI) on the risk of all lung-cancer subtypes was larger than additive (RERI = 2.10; 95% CI 1.41-2.79; Table 5). RERI was particularly high for squamous-cell and small-cell cancer of the lung (Table S8). For women, these associations were similar, however estimates were less precise compared to men (Tables 5 and S8). When using a multiplicative model as framework, no statistical significance for the interaction term in the model was observed except for small-cell lung cancer in men, implying that

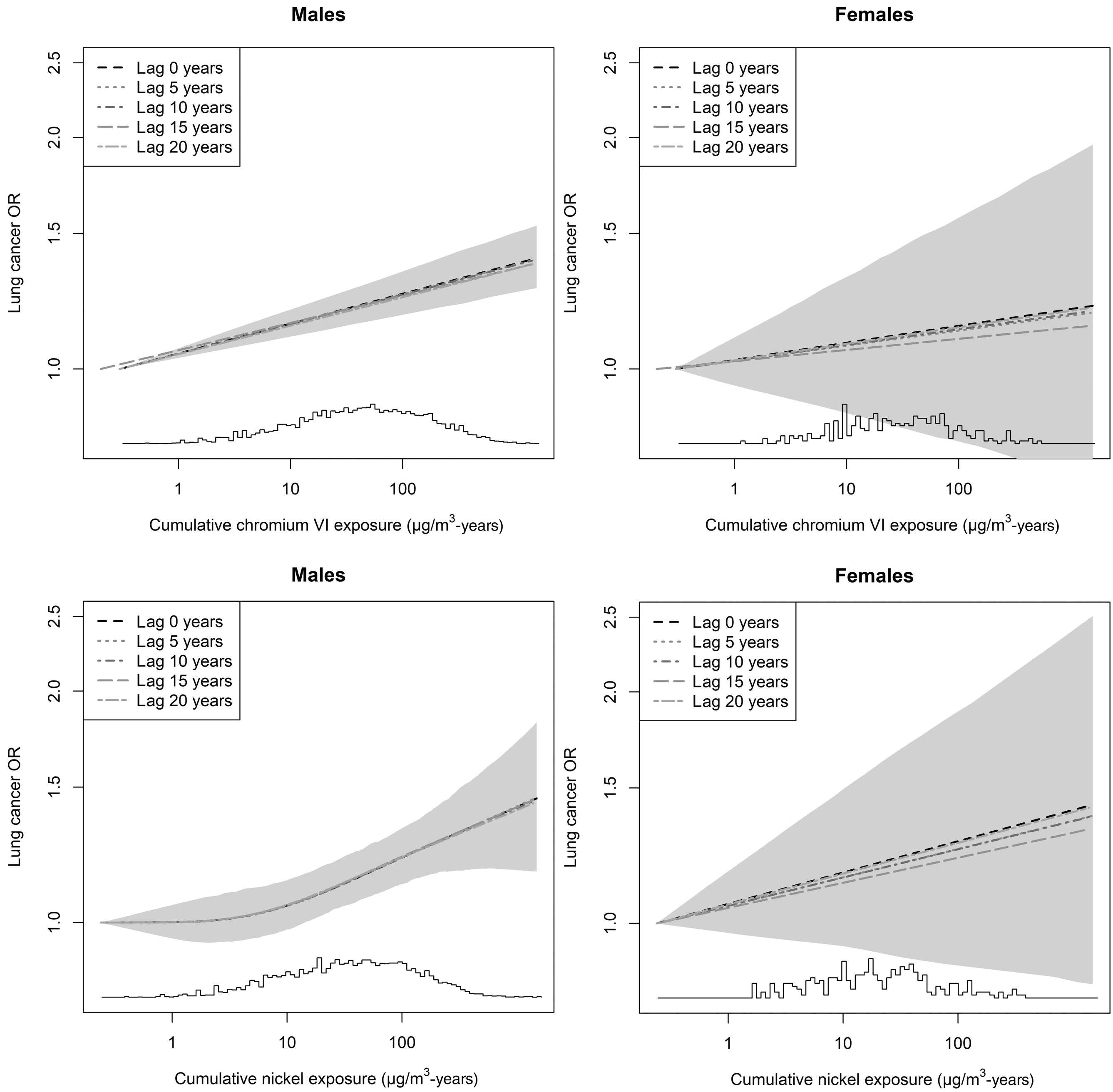

FIGURE 1 Exposure-response relationships among males and females for cumulative hexavalent chromium and nickel exposure with different lag periods, adjusted for study, age group, cigarette pack-years, time-since-quitting smoking and ever employment in a "list A" job. The histograms on the x-axis show the distribution of the cumulative exposure in the respective subpopulations

TABLE 5 Lung-cancer odds ratios and 95% CI, *P*-value for multiplicative interaction and relative excess risk due to interaction (RERI) and 95% CI in relation to occupational chromium (VI) and nickel exposure and smoking among men and women

	Men					Women				
Exposure status	**Cases**	**Controls**	**OR[a]**	**95% CI**	**99.4% CI[b]**	**Cases**	**Controls**	**OR[a]**	**95% CI**	**99.4% CI[b]**
Chromium (VI)										
Never smoker and never Cr(VI)	374	3592	1.0	Ref.	Ref.	844	2640	1.0	Ref.	Ref.
Never smoker and Cr(VI)	116	845	1.22	0.98-1.53	0.89-1.68	35	76	1.13	0.73-1.73	0.62-2.08
Ever smoker and never Cr(VI)	9100	9039	9.31	8.34-10.42	7.95-10.89	2293	1728	4.77	4.29-5.31	4.10-5.55
Ever smoker and ever Cr(VI)	4015	2975	11.63	10.34-13.11	9.83-13.75	124	70	6.22	4.54-8.57	3.97-9.73
P-value multiplicative interaction			.86					.60		
RERI with linear model[c]			2.10	1.41-2.79				1.31	−0.66-3.29	
Nickel										
Never smoker and never nickel	402	3735	1.0	Ref.	Ref.	847	2650	1.0	Ref.	Ref.
Never smoker and nickel	88	702	1.08	0.84-1.38	0.76-1.53	32	66	1.27	0.80-1.97	0.67-2.39
Ever smoker and never nickel	9987	9576	9.31	8.37-10.38	7.99-10.84	2298	1733	4.77	4.29-5.31	4.10-5.55
Ever smoker and ever nickel	3128	2438	10.63	9.46-11.98	9.00-12.56	119	65	6.60	4.78-9.18	4.16-10.46
P-value multiplicative interaction			.66					.76		
RERI with linear model[c]			1.25	0.56-1.93				1.56	−0.60-3.72	

[a]OR adjusted for study, age group and "list A" jobs.
[b]99.4% CI Bonferroni-corrected for nine subtests.
[c]Confidence intervals are based on 1000 bootstrap samples.

there is no significant deviation of the joint effect between smoking and occupational exposure to Cr(VI) or nickel from multiplicativity (Tables 5 and S8). Analysis of the interaction between Cr(VI) and nickel exposure was impaired by a high correlation between these agents, and, as stated above, we refrained from adjusting mutually for the other metal in these analyses.

Although the main analyses contained only one of the two exposure variables of interest, we conducted a set of sensitivity analyses that mutually adjusted for both, Cr(VI) and nickel. The OR for Cr(VI) was similar in the two-variable model compared to the one-variable model. By contrast there was some difference between the two models for the OR estimate for nickel. In men, ORs for nickel were attenuated to OR = 1.05; 95% CI 0.97-1.14 and ORs for women slightly increased (OR = 1.39; 95% CI 0.99-1.94). Analysis of subjects solely exposed to Cr(VI), but not nickel yielded an OR of 1.40; 95% CI 1.25-1.57 for men and 0.59; 95% CI 0.24-1.42 for women, but the latter analysis was based on only 10 exposed cases and 15 exposed controls. Subjects solely exposed to nickel were too few to conduct a sound sensitivity analysis (four male cases and three controls, but no exposed female case subject, all results not shown).

4 | DISCUSSION

We studied the associations between occupational Cr(VI) and nickel exposure with lung cancer in the pooled SYNERGY case-control study. Increasing duration and increasing cumulative exposure to Cr(VI) or nickel were associated with increasing ORs for lung cancer. As it can be expected from welding and various metalwork-related activities,[1] Cr(VI) and nickel exposures were highly correlated in our data so that we did not adjust mutually for both metals in our analyses. Increased risks for Cr(VI) and nickel were found in never smokers, former smokers and current smokers. The joint effect of smoking and Cr(VI) or nickel exposure was generally more than additive, particularly for squamous-cell and small-cell cancer of the lung. All these effects were clearly seen in men with narrow confidence intervals. Women showed similar risks, but analyses were limited by smaller numbers of exposed subjects, and subsequently analyses yielded wider confidence intervals in ever-never comparisons and exposure-effect trends.

Hexavalent chromium and at least some forms of nickel compounds are established lung carcinogens which have been repeatedly evaluated by IARC.[1,2,11,30,31] IARC's classification as Group 1 carcinogens relied mainly on industrial cohort studies of chromium production and nickel refinery workers.

Two of the largest chromium cohorts from Baltimore, MD, and Painsville, OH, have been repeatedly updated and reanalyzed with respect to lung-cancer risk. These studies unanimously indicated some increase in lung-cancer risk with respect to occupational Cr(VI) exposure.[12,32-35] We here add to the evidence by supporting these observations with analyses in a large pooled case-control study.

Although the exact nickel compounds responsible for an increased lung-cancer risk are unknown, results of studies among Norwegian refinery workers, suggest the strongest evidence for total nickel and water-soluble nickel compounds.[2,14,36] Additional analyses of this Norwegian cohort revealed a clear dose-effect relationship with lung-cancer risk for water-soluble compounds, but little support for metallic, oxidic or sulfidic forms of nickel as risk factors, when mutually adjusting for water-soluble nickel compounds.[36] Although epidemiological studies are limited in disentangling, which form is associated with an increased lung-cancer risk due to exposure to multiple forms of nickel, our findings in SYNERGY compare well with findings from these cohorts (see OR1 in Table 2). However, exposure levels were in general lower than in these industries.

More recently, a semi-quantitative approach was undertaken by a population-based Canadian case-control study, whose data partially also contributed to this analysis. The study also showed increased lung-cancer risks in relation to occupational Cr(VI) or nickel exposure, but only among nonsmokers and former smokers quitting smoking over 20 years prior to inclusion into the study.[37] This finding is probably due to the strong effects of smoking on lung-cancer risk, leading to relative risks for occupational exposures being superimposed by the higher risk for lung cancer from smoking.

The median cumulative exposure level of 40 $\mu g/m^3$-years for Cr(VI) observed in our study corresponds with the current SCOEL benchmark value of 1 $\mu g/m^3$ associated with 4/1000 excess lung-cancer cases during 40 years of working life,[7] indicating that in the past a substantial part of the occupational workforce was exposed to Cr(VI) above these levels. The SCOEL benchmark value[7] was based on the mean value from the individual slope estimates of $\beta = 1.75$,[38] as derived from the studies by Crump and coworkers ($\beta = 0.68$)[12] and Park et al. ($\beta = 2.82$).[33] Kauermann and others,[39] using a variety of model specifications, derived a combined slope estimate of 0.63 based on a pooled analysis of aggregated data from these studies. Using these two reported slope estimates, we can calculate an expected relative risk of 1.19 and 1.07 for men at an exposure level of 0.1 mg/m^3-years, respectively, which is in line with our finding of an OR of 1.24 at this exposure level. In contrast, median cumulative nickel concentrations in SYNERGY (20 $\mu g/m^3$-years) were much lower than the current SCOEL threshold limit value of 10 $\mu g/m^3$, if taking into account a 40-year occupational exposure period.

Strengths of our analysis include a large study population with sufficient power to detect potentially increased risks in subgroups such as women, nonsmokers, and for histological lung-cancer subtypes, while taking into account detailed information on smoking habits. The use of a database of measurements from different countries and industries and modeling of an exposure time trend enabled us to assess cumulative exposures over the entire job histories and across jobs and industries quantitatively.[23]

Although we included a high number of personal measurements to assess occupational exposure to Cr(VI) and nickel, limitations related to exposure assessment are that the measurements for a particular job did not necessarily correspond with the jobs reported in the study subjects' occupational history.[23] This will cause some degree of measurement error of the Berkson type, which will primarily weaken the precision of our estimates. Likely, the effect on point estimates will be rather small and lead to attenuation of ORs.[40] However, we cannot rule out the possibility of a combined error structure of classical measurement and Berkson-type of error, which may occur when estimating quantitative exposure-effect associations using random exposure-grouping methods. This is frequently the case in job-exposure matrices in which exposure levels are estimated for various occupational groups instead a fixed occupational setting. This situation may cause a nondifferential measurement error turning into differential bias, thus leading to over- or underestimation of risk estimates. As it has been shown, decreasing between-group variance usually leads to an increase in bias, which may also have affected our estimates that were situated in the low-exposure range.[26]

Exposure assessment in SYNERGY was performed to capture a wide array of exposed jobs, which may have resulted in assigning exposure levels to subjects who were only occasionally exposed to Cr(VI) or nickel or not at all. We therefore cannot rule out that our risk estimates, at least partially, entail a "blue-collar" effect associated with multiple exposures to several occupational carcinogens. Restricting analyses to blue-collar workers, indeed revealed reduced ORs compared to the full sample. In addition, the relatively low response proportions in many of the population-based case-control studies may have resulted in a general underrepresentation of blue-collar workers in the control group, potentially inflating the observed associations when including white-collar workers. However, positive associations were seen for the highest exposure groups, and trends across exposure categories were consistent.

5 | CONCLUSIONS

Summarizing, we observed positive exposure-effect associations between lung-cancer risk and occupational exposure to Cr(VI) and to nickel in the large SYNERGY study in men. Women showed similar tendencies, albeit with less statistical precision due to the smaller numbers of exposed female subjects. We estimated exposure-risk relationships over a wide range of exposed jobs, using a comprehensive measurement-based JEM. Among men, increased lung-cancer risks were associated with both longer exposure duration and higher cumulative exposure to Cr(VI) or nickel. Similar results were also observed across smoking group strata. The joint effect of smoking and Cr(VI) or nickel generally exceeded additivity. Various sensitivity analyses corroborated the robustness of these results. Although differential bias in our results due to combined Berkson and classical error structure cannot be ruled out, our results warrant a continuing awareness to monitor the impact of occupational metal exposure on human cancer by epidemiologic, toxicological and experimental investigations.

AUTHOR CONTRIBUTIONS

Kurt Straif, Thomas Brüning, Hans Kromhout and Roel Vermeulen contributed to the original conception and acquired funding for the project. Kurt Straif, Joachim Schüz, Hans Kromhout, Roel Vermeulen, Ann Olsson, Beate Pesch, Thomas Brüning and Thomas Behrens developed the methodology for this analysis. Thomas Behrens wrote the draft, by integrating suggestions from Calvin Ge, Ann Olsson, Susan Peters, Joachim Schüz, Kurt Straif, Hans Kromhout, Roel Vermeulen, Beate Pesch and Jack Siemiatycki. Calvin Ge, Benjamin Kendzia and Lützen Portengen conducted the formal statistical analyses. Jack Siemiatycki, Marie-Elise Parent, Per Gustavsson, Paolo Boffetta, Pascal Guénel, Danièle Luce, Stefan Karrasch, Heinz-Erich Wichmann, Maria Teresa Landi, Neil E. Caporaso, Dario Mirabelli, Lorenzo Richiardi, Dario Consonni, Lorenzo Simonato, Karl-Heinz Jöckel, Wolfgang Ahrens, Hermann Pohlabeln, Guillermo Fernández-Tardón, David Zaridze, John K. Field, Jolanta Lissowska, Beata Świątkowska, John R. McLaughlin, Paul A. Demers, Vladimir Bencko, Lenka Foretova, Vladimír Janout, Tamás Pándics, Eleonora Fabianova, Dana Mates, Francesco Forastiere and Bas Bueno-de-Mesquita participated in data acquisition, design and quality assurance of the original study data. Data curation of the pooled data (annotation, data cleaning and maintaining research data) was done by Ann Olsson, Benjamin Kendzia, Susan Peters and Lützen Portengen. All authors participated in critical revision of the manuscript and provided approval of the finalized submitted version. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

None reported.

DATA AVAILABILITY STATEMENT

The data are from a pooled study, and the data right owners are the individual study groups whose authors may be contacted at synergy@iarc.fr. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The IARC Institutional Review Board provided ethical approval for the pooled study, while national ethics committees approved the local case-control studies. All study subjects gave written informed consent.

ORCID

Thomas Behrens https://orcid.org/0000-0002-4583-5234
Joachim Schüz https://orcid.org/0000-0001-9687-2134
Pascal Guénel https://orcid.org/0000-0002-8359-518X
Marie-Elise Parent https://orcid.org/0000-0002-4196-3773

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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