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Original Contribution

Exposure to Welding Fumes, Hexavalent Chromium, or Nickel and Risk of Lung Cancer

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To investigate the risk of lung cancer after exposure to welding fumes, hexavalent chromium (Cr(VI)), and nickel, we analyzed 3,418 lung cancer cases and 3,488 controls among men from 2 German case-control studies (1988–1996). We developed a welding-process exposure matrix from measurements of these agents, and this was linked with welding histories from a job-specific questionnaire to calculate cumulative exposure variables. Logistic regression models were fitted to estimate odds ratios with confidence intervals conditional on study, and they adjusted for age, smoking, and working in other at-risk occupations. Additionally, we mutually adjusted for the other exposure variables under study. Overall, 800 cases and 645 controls ever worked as regular or occasional welders. Odds ratios for lung cancer with high exposure were 1.55 (95% confidence interval (CI): 1.17, 2.05; median, 1.8 mg/m^3 × years) for welding fumes, 1.85 (95% CI: 1.35, 2.54; median, 1.4 μg/m^3 × years) for Cr(VI), and 1.60 (95% CI: 1.21, 2.12; median, 9 μg/m^3 × years) for nickel. Risk estimates increased with increasing cumulative exposure to welding fumes and with increasing exposure duration for Cr(VI) and nickel. Our results showed that welding fumes, Cr(VI), and nickel might contribute independently to the excess lung cancer risk associated with welding. However, quantitative exposure assessment remains challenging.

metals; occupation; smoking; welders

Abbreviations: AUT, Arbeit und Technik; CI, confidence interval; Cr, chromium; Cr(VI), hexavalent chromium; HdA, Humanisierung des Arbeitslebens; Ni, nickel; OR, odds ratio; WEM, welding exposure matrix.

It has been estimated that approximately 120 million workers worldwide are regularly or occasionally exposed to welding fumes (1). Welding is a primary industrial process for joining metal parts, and welding fumes have been classified as carcinogenic to humans (2). In past epidemiologic studies, exposure to welding fumes was frequently assessed through job title and duration of welding (3–8). Although different welding processes generate different mixtures of particulate matter and metals (9, 10), excess relative risks were observed for lung cancer regardless of the welding technique or type of steel (11). Little is known about the respective contributions of different constituents of welding fumes in the development of lung cancer.

There have been a few attempts to develop job-exposure matrices that could be used to quantitatively estimate exposure to welding-related agents. The Finnish job-exposure matrix was applied to calculate the exposure to welding fumes and iron in Finnish men (12). A more detailed welding exposure matrix (WEM) was developed for a cohort of European welders with process-specific estimates of exposure to welding fumes, chromium (Cr), hexavalent Cr (Cr(VI)), and nickel (Ni) (13). Measurements were derived primarily from existing literature on welding (14). Another WEM was developed for the exposure to welding fumes in a Danish cohort of welders, using more than 1,000 measurements, but exposure to Ni or Cr was not included (15).

The present study was conducted to estimate the lung cancer risk associated with exposure to welding fumes, Cr(VI), and Ni among workers reporting regular or occasional welding in a pooled analysis of 2 population-based German case-control studies. Exposure to these agents was assessed by substituting the original shift concentrations of the WEM that was developed for the European cohort of welders with estimates derived from measurements at German workplaces (9, 10, 16–18). This WEM was linked to individual welding histories that were acquired from a welding-specific questionnaire to estimate the lung cancer risk in relation to cumulative exposure to welding fumes, Cr(VI), and Ni.

METHODS

Study population

We estimated the lung cancer risk of welding using data from 3,418 male cases and 3,488 controls in 2 population-based German case-control studies, which were pooled within the framework of the SYNERGY project (http://synergy.iarc.fr) to study lung cancer risks of occupational carcinogens. The studies are Humanisierung des Arbeitslebens (HdA) (3) and Arbeit und Technik (AUT) (19). Detailed descriptions of the 2 studies have been previously published (3, 19). Following are brief summaries of the designs.

For the HdA Study, 1,004 incident cases of lung cancer in men and women and 1,004 population controls were interviewed between 1988 and 1993, with a response proportion of 69% for cases and 68% for controls. Controls were matched 1:1 to cases by sex, age (within 5 years), and region of residence. Classification of histological subtypes was checked against the reference pathology according to World Health Organization guidelines (20). For the AUT Study, 3,180 incident cases in men and women and 3,249 population controls were interviewed with similar matching criteria between 1990 and 1996. The response was 77% among cases and 41% among controls. Ethical approvals were obtained in accordance with German legislation and by the ethics committee of the International Agency for Research on Cancer.

Data collection and exposure assessment

In both studies the data were collected from personal interviews that focused on the subject's job history. Job titles were coded according to the International Standard Classification of Occupations, version 1968 (21). As part of that original questionnaire, there was a supplemental questionnaire for all participants of both studies who ever performed welding, regardless of the job title, regarding welding techniques, materials used, the work environment, and use of exhaust ventilation (3).

Ten welding techniques and 4 materials (mild steel, stainless steel, Cr/Ni alloys, and aluminum) were classified according to the structure of the WEM (Web Table 1, available at https://academic.oup.com/aje). Welding activities were classified as "regular" if they occurred every day in the job; otherwise they were classified as "occasional." Occasional welding was calibrated to regular welding with the following weights: 2–4 times per week = 0.25; once per week = 0.1; 1–3 times per month = 0.05; lower frequencies = 0.025. Both studies used the same questionnaire, but HdA additionally documented "welding hours," with a median of 3 hours for occasional welding. Full-shift exposure was assumed for regular welding; otherwise, 3 hours for occasional welding. Subjects who reported that they simultaneously performed several welding processes were additionally weighted with regard to the time using these techniques.

We substituted the shift concentrations in the WEM of the European cohort of welders (13) using the estimates from personal measurements of inhalable welding fumes (n = 15,473), Cr(VI) (n = 1,898), and Ni (n = 3,055) that were compiled in the exposure database Messdaten zur Exposition gegenüber Gefahrstoffen am Arbeitsplatz (MEGA) (Web Table 1) (16–18). Measurements below the limit of detection or quantitation (welding fumes: 23%; Cr(VI): 61%; Ni: 22%) were multiply imputed to estimate the geometric means as a proxy of the average annual shift concentrations. Because Cr(VI) and Ni were preferentially measured when welding stainless steel, we also considered measurements when welding mild steel in 2 studies (9, 10). Linking the individual welding histories to this WEM generated annual estimates of average shift concentrations of welding fumes, Cr(VI), and Ni. Cumulative exposure was expressed as "concentration × years" for each agent, by summarizing all periods with welding activities. Web Figure 1 shows the distribution of measurements over time compared with welding in this study.

In order to distinguish metal exposures in welding from those in basic metal production, we separated out those 131 men who were smelters (comprising the 3-digit codes 721 and 723 of the International Standard Classification of Occupations (ISCO-68)) as a separate group to analyze. The reference group comprised men who never worked in welding or smelting.

Statistical analyses

We estimated the lung cancer risks of the agents under study, for the welding process (including steel grade and workplace conditions), and for time since last exposure (9, 22). The cumulative exposure variables were categorized according to tertiles of the distribution in exposed controls, and into low or high exposure using the median for certain stratified analyses. In order to investigate the association between welding and lung cancer, logistic regression models were fitted to estimate odds ratios and 95% confidence intervals conditional on study and adjusted for covariates. Additionally, we fitted unconditional models. Model 1 adjusted for log(age); model 2 additionally adjusted for log(pack-years + 1); time since quitting (current smokers; stopping smoking 2–7, 8–15, 16–25,or ≥26 years before diagnosis or interview; ever other types of tobacco (pipes, cigars) only; never smokers). Model 3 adjusted for employment in jobs with an anticipated lung cancer risk, except for those with exposure to metal fumes (4, 23, 24). Where appropriate, we mutually adjusted the risk estimate of one agent for the individual average intensity of exposure to the other agents under study (model 4). Due to the correlation between Cr(VI) and Ni concentrations (Spearman correlation coefficient = 0.83; 95% confidence interval (CI): 0.78, 0.88), we made final adjustments for welding fumes only (model 5).

We assessed statistical significance (1-sided) of trends in exposure-response relationships with and without unexposed men, using a logistic regression model applied to the log-transformed continuous exposure variables. In order to investigate the shape of the dose-response relationship, we performed adjusted restricted cubic splines using nonparametric smoothing with knots at the 25th, 50th, 75th, and 95th percentile of the distribution of exposure variables among the exposed controls. The confidence limits for odds ratios were derived by simulating the posterior distribution of the model coefficients, performing random draws from a multivariate normal distribution parameterized by the estimated mean vector and estimated covariance matrix of the model coefficients.

We tested departure from multiplicative interactions between exposure variables and pack-years of cigarette smoking, and we investigated the combinations of high and low exposure, as well as of duration and intensity of exposure to the agents under study.

Robustness of results was examined by sensitivity analyses as follows: stratified by study; restricting the exposed subjects to the job title "welder" in order to limit potential uncertainties of the exposure assessment in occasional welders; restricting subjects with welding activities to those who never worked as a smelter, to limit uncertainties of the cancer risk from exposure to metal fumes in other settings; restricting the study group to blue-collar workers, to limit residual confounding from socioeconomic factors; and lagging exposure by disregarding exposure in the last 10 years before diagnosis or interview.

Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Characteristics of the study groups are shown in Table 1: 396 cases and 277 controls reported ever regular welding and another 404 cases and 368 controls reported occasional welding. Both cases and controls started welding at a median age of 17 years. Compared with the controls, cases were more often smokers and exposed to carcinogens in other occupations. Smelters and those who worked in other at-risk occupations had the highest smoking prevalence. The distribution of lung-cancer cell types did not vary by study group, except for smelters, who had a lower fraction of adenocarcinoma.

Lung cancer risk according to welding-related factors

Table 2 presents the risk estimates for lung cancer associated with welding, reported as fully adjusted odds ratios unless otherwise stated. Ever regular welding was associated with a higher lung cancer risk (odds ratio (OR) = 1.37, 95% CI: 1.14, 1.65) than was occasional welding (OR = 1.19, 95% CI: 1.00, 1.42). Short-time welding was shown to be associated with elevated lung cancer risk (1.5–9 years, OR = 1.39; 95% CI: 1.12, 1.72). The median age of the last welding was 39 years among cases and 36 years among controls. We observed a decreasing trend relative to time since last exposure ($P = 0.009$), ranging from an odds ratio of 1.72 (95% CI: 1.26, 2.36) for current welding to an odds ratio of 0.87 (95% CI: 0.64, 1.17) after ≥40 years.

Major welding processes were associated with an increased risk of lung cancer, as shown in Table 2, for applications of ≥5 years (autogenous welding, OR = 1.33, 95% CI: 1.13, 1.56; manual metal arc welding, OR = 1.32, 95% CI: 1.14, 1.55; torch cutting, OR = 1.35; 95% CI: 1.13, 1.62), and in Web Table 2 for ever using these processes, as well as for ≥10 years, indicating increased risks by duration of exposure. We observed no clear difference between the steel grades (ever welding of mild steel, OR = 1.28; 95% CI: 1.11, 1.46; stainless steel, OR = 1.27; 95% CI: 0.97, 1.65). Seven men exclusively welded stainless steel, and 22 men ever welded aluminum. We observed an elevated risk for those welding without local exhaust ventilation (OR = 1.36, 95% CI: 1.16, 1.58).

Exposure-response relationship for welding fumes, Cr(VI), and Ni

Increasing cumulative exposure to these agents was associated with higher risks, when stratified by the respective median values in exposed controls or when nonexposed subjects were included in linear trend tests as shown in Table 3. The estimated lung cancer risks of welding fumes, Cr(VI), and Ni exposure were even stronger when mutually adjusted for the concentrations of the other agents (model 4, for exposure above the median values: welding fumes, OR = 1.55, 95% CI: 1.17, 2.05; Cr(VI), OR = 1.85, 95% CI: 1.35, 2.54; Ni, OR = 1.60, 95% CI: 1.21, 2.12). Similar odds ratios were estimated with unconditional models (Web Table 3). Furthermore, we adjusted Cr(VI) and Ni for the concentration of welding fumes only, with similar risk estimates for Ni and slightly lower odds ratios for Cr(VI). Assuming a 3% annual reduction of welding fume concentrations since 1960 resulted in an odds ratio of 1.47 (95% CI: 1.09, 1.95) for exposure above the median (Web Table 4).

Linear trends were also calculated within the exposed subjects only, with a P value of 0.03 for cumulative exposure to welding fumes. No obvious trends were observed for Cr(VI) and Ni, with indication of a nonlinear shape of the dose-response relationship (Web Figure 2).

In Table 4, we present risk estimates for combinations of shift concentrations in relation to the duration of exposure, which was assessed as "welding years" by considering the lower time in occasional welding, in order to separate the dimensions of the cumulative exposure metric. We observed no risk increase at higher concentrations but a strong time trend for Cr(VI) and Ni. Five or more welding years were associated with odds ratios of approximately 3.5 for both metals at low as well as at high average concentrations.

Joint risks of welding fumes in combination with Cr(VI) and Ni

Web Table 5 presents the risk estimates of low or high cumulative exposure to welding fumes in combination with low or high metal exposure, stratified by their median values in exposed controls. The risk estimates (here model 3) were 1.08 (95% CI: 0.88, 1.31) for low exposure to all agents and 1.39 (95% CI: 1.16, 1.65) for high exposure to these agents. Low welding fume exposure in combination with high levels of Cr(VI) or Ni was associated with an odds ratio of 1.59 (95% CI: 0.78, 3.27), with 1.77 (95% CI: 0.97, 3.24) for the opposite combination; however, these odds ratios were based on small numbers.

Lung cancer risks of welding fumes, Cr(VI), and Ni stratified by smoking

Table 5 presents the odds ratios for exposure to these agents in never, light (1–9.99 pack-years), medium (10–34.99 pack-years), and heavy (≥35 pack-years) smokers. Referents were nonexposed men in the respective smoking category. We observed only 13 exposed cases among never smokers. In all other groups, the odds ratios for men with exposure above the median values

Table 1. Characteristics of the Study Population According to Exposure to Welding Fumes and Disease Status, Arbeit und Technik Study and Humanisierung des Arbeitslebens Study, Germany, 1988–1996

Characteristic	Regular Welding				Occasional Welding				Smelters				Not Exposed to Metal Fumes[a]			
	Cases		Controls		Cases		Controls		Cases		Controls		Cases		Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of male participants	396	11	277	8	404	12	368	10	80	2	51	1	2,618	75	2,843	80
Study																
HdA	124	31	91	33	113	28	101	27	12	15	9	18	590	23	636	22
AUT	272	69	186	67	291	72	267	73	68	75	42	72	2,028	77	2,207	78
Age, years																
<45	36	9	8	3	26	6	28	8	0	0	1	2	125	5	166	6
45–64	267	67	188	68	270	67	241	65	64	80	38	75	1,628	62	1,789	63
≥65	93	23	81	29	108	27	99	27	16	20	12	23	865	33	888	31
Cigarette smoking																
Never	6	2	49	18	7	2	80	22	2	3	3	6	52	2	654	23
Former	116	29	134	48	130	32	178	48	26	33	25	49	948	36	1,387	49
Current	269	68	90	32	259	64	97	26	51	64	20	39	1,580	60	698	25
Other types of tobacco	5	1	4	1	8	2	13	4	1	1	3	6	35	1	104	4
Smoking, pack-years																
1.00–9.99	25	6	56	25	31	8	84	29	6	8	12	24	205	8	653	30
10.00–34.99	191	49	119	52	192	48	141	49	31	39	27	53	1,122	44	1,071	49
≥35.00	174	45	53	23	174	44	63	22	41	51	9	18	1,239	48	465	21
Time since quitting smoking, years																
<8	43	11	16	6	49	12	25	7	8	31	5	20	344	13	212	7
8–15	31	8	30	11	31	8	40	11	9	35	3	12	249	10	306	11
16–24	25	6	35	13	27	7	54	15	6	23	6	24	217	8	438	15
≥25	17	4	53	19	23	6	59	16	3	12	11	44	138	5	432	15
At-risk occupations[b]																
Never	337	85	254	92	345	85	331	90	44	55	33	65	2,225	85	2,563	90
Ever	59	15	23	8	59	15	37	10	36	45	18	35	393	15	280	10
Histological subtype																
Adenocarcinoma	69	17			71	18			9	11			459	18		
Squamous cell carcinoma	165	42			170	42			43	54			1,226	47		
Small cell lung cancer	105	27			98	24			15	19			591	23		
Other or mixed	57	14			65	16			13	16			342	12		

Abbreviations: AUT, Arbeit und Technik; HdA, Humanisierung des Arbeitslebens.
[a] Subjects who were never exposed to metal fumes from welding or smelting.
[b] Occupations involving risk of lung cancer, except in those with exposure to hot metal fumes, based on prior work (4, 23, 24).

were higher than among those with lower exposure levels and highest in light smokers (model 4, for welding fumes, OR = 2.79, 95% CI: 1.27, 6.13; Cr(VI), OR = 4.48, 95% CI: 1.84, 10.9; Ni, OR = 3.94, 95% CI: 1.64, 9.44). There was no obvious multiplicative interaction between cumulative exposures to these agents with pack-years.

Sensitivity analyses

Web Table 6 shows rather robustly that exposure above the median values was associated with increased risk estimates in all sensitivity analyses, with some exceptions for Cr(VI) and Ni, in particular with regular welding. Restricting the study population to blue-collar workers slightly attenuated the risk estimates. The exclusion of smelters or lagging exposure time by 10 years did not obviously alter the odds ratios.

DISCUSSION

Findings of elevated lung cancer risk in epidemiologic studies (4, 5, 12, 15, 25, 26) provided sufficient evidence for the

Table 2. Lung Cancer Risk Among Workers in Welding-Related Occupations, Arbeit und Technik Study and Humanisierung des Arbeitslebens Study, Germany, 1988–1996

Welding Activity	No. of Cases	No. of Controls	Model 1		Model 2		Model 3	
			OR[a]	95% CI	OR[b]	95% CI	OR[c]	95% CI
Reference group[d]	2,618	2,843	1.00	Referent	1.00	Referent	1.00	Referent
Ever working as smelter	80	51	1.70	1.19, 2.43	1.30	0.88, 1.93	1.19	0.80, 1.77
Ever occasional welding	404	368	1.20	1.03, 1.39	1.19	1.00, 1.42	1.19	1.00, 1.42
Ever regular welding	396	277	1.56	1.33, 1.84	1.37	1.14, 1.65	1.37	1.14, 1.65
Duration of welding, years								
<1.5	214	214	1.21	1.02, 1.44	1.13	0.93, 1.38	1.10	0.90, 1.35
1.5–9.9	280	205	1.48	1.23, 1.79	1.40	1.13, 1.74	1.39	1.12, 1.72
≥10.0	306	226	1.49	1.24, 1.78	1.32	1.08, 1.63	1.34	1.09, 1.65
P value[e]			0.22		0.21		0.18	
P value[f]			0.20		0.32		0.25	
Time since last welding, years								
Current welding	147	88	1.89	1.44, 2.48	1.71	1.25, 2.34	1.72	1.26, 2.36
1.0–9.9	151	123	1.34	1.05, 1.71	1.27	0.96, 1.68	1.28	0.97, 1.69
10.0–24.9	195	142	1.52	1.21, 1.90	1.32	1.03, 1.71	1.32	1.02, 1.67
25.0–39.9	196	170	1.26	1.02, 1.56	1.29	1.01, 1.65	1.31	1.02, 1.67
≥40.0	111	122	0.96	0.74, 1.25	0.87	0.64, 1.17	0.87	0.64, 1.17
P value[e]			0.004		0.007		0.009	
Welding process used ≥ 5 years								
Autogenous welding	513	409	1.36	1.18, 1.56	1.31	1.12, 1.54	1.33	1.13, 1.56
Spot welding	140	111	1.38	1.07, 1.79	1.27	0.95, 1.71	1.29	0.96, 1.73
Manual metal arc welding	493	387	1.38	1.19, 1.59	1.31	1.11, 1.54	1.32	1.14, 1.55
Torch cutting	407	305	1.44	1.23, 1.69	1.34	1.21, 1.61	1.35	1.13, 1.62
Arc spraying	24	16	1.64	0.87, 3.09	1.92	0.94, 3.93	1.94	0.95, 3.96
Gas metal arc welding	76	56	1.51	1.06, 2.14	1.38	0.92, 2.07	1.39	0.93, 2.08
Tungsten inert gas welding	36	28	1.43	0.87, 2.35	1.24	0.71, 2.16	1.22	0.70, 2.14
Ever used as consumable material								
Mild steel	775	619	1.35	1.20, 1.52	1.27	1.11, 1.45	1.28	1.11, 1.46
Stainless steel	180	136	1.45	1.15, 1.83	1.24	0.95, 1.62	1.27	0.97, 1.65
Cr/Ni alloys	66	50	1.43	0.99, 2.08	1.29	0.85, 1.95	1.30	0.86, 1.97
Workplace conditions								
Nonconfined space	629	531	1.29	1.14, 1.47	1.25	1.08, 1.45	1.25	1.08, 1.45
Confined space	166	113	1.63	1.27, 2.08	1.29	0.98, 1.71	1.30	0.99, 1.72
Local exhaust ventilation	189	175	1.19	0.96, 1.48	1.06	0.83, 1.35	1.06	0.83, 1.35
No local exhaust ventilation	596	457	1.42	1.24, 1.63	1.35	1.16, 1.58	1.36	1.16, 1.58

Abbreviations: CI, confidence interval; Cr, chromium; Ni, nickel; OR, odds ratio.
[a] Adjusted for log(age) and conditional on study.
[b] Additionally adjusted for log(pack-years + 1), time since quitting smoking cigarettes (current smokers; ever other types of tobacco (pipes, cigars) only; stopped smoking 2–7, 8–15, 16–25, or ≥26 years before interview or diagnosis; never smokers).
[c] Additionally adjusted for ever working in at-risk jobs except in those with exposure to hot metal fumes.
[d] Subjects who were never exposed to metal fumes from welding or smelting.
[e] *P* for trend values were computed by entering the continuous variable (duration of employment or years since last welding) into the model.
[f] *P* for trend values were computed by entering the duration of employment restricted to exposed men into the model.

classification of welding as carcinogenic to humans (1, 2) regardless of the welding process and materials welded (11). Some studies quantified exposure to welding fumes or metals but could not demonstrate dose-response relationships (12, 13, 15). It is still unresolved which constituents confer the greatest risk. We observed increased risks

Table 3. Lung Cancer Risks of Welding-Related Occupations for Cumulative Exposure to Welding Fumes, Hexavalent Chromium, or Nickel in Men With Welding Activities, Arbeit und Technik Study and Humanisierung des Arbeitslebens Study, Germany, 1988–1996

Cumulative Exposure	No. of Cases	No. of Controls	Model 1		Model 2		Model 4		Model 5	
			OR[a]	95% CI	OR[b]	95% CI	OR[c]	95% CI	OR[d]	95% CI
Reference group[e]	2,618	2,843	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Welding fumes[f]										
In tertiles										
≤629	208	210	1.08	0.89, 1.32	1.04	0.83, 1.30	1.09	0.80, 1.48		
630–4,721	293	215	1.48	1.24, 1.79	1.46	1.18, 1.81	1.55	1.15, 2.09		
≥4,722	299	220	1.48	1.24, 1.78	1.31	1.06, 1.61	1.40	1.03, 1.89		
High/low exposure										
≤1,837	352	322	1.19	1.02, 1.40	1.11	0.92, 1.33	1.18	0.89, 1.55		
≥1,838	448	323	1.51	1.30, 1.76	1.44	1.21, 1.71	1.55	1.17, 2.05		
P value[g]			0.004		0.012		0.047			
P value[h]			0.06		0.03		0.03			
Cr(VI)[f]										
In tertiles										
≤0.49	200	213	1.05	0.86, 1.28	1.00	0.80, 1.25	1.12	0.84, 1.49	1.01	0.81, 1.27
0.50–3.69	336	212	1.59	1.32, 1.91	1.52	1.23, 1.88	1.87	1.37, 2.54	1.67	1.33, 2.09
≥3.70	264	220	1.43	1.19, 1.71	1.30	1.06, 1.61	1.75	1.22, 2.51	1.53	1.18, 1.97
High/low exposure										
≤1.39	347	323	1.17	1.00, 1.38	1.12	0.93, 1.34	1.29	0.99, 1.68	1.16	0.96, 1.40
≥1.40	453	322	1.53	1.32, 1.79	1.42	1.19, 1.70	1.85	1.35, 2.54	1.63	1.31, 2.02
P value[g]			<0.0001		0.009		0.095		0.010	
P value[h]			0.04		0.70		0.52		0.42	
Ni[f]										
In tertiles										
≤2.99	217	212	1.12	0.92, 1.36	1.05	0.84, 1.32	1.07	0.82, 1.40	1.07	0.85, 1.34
3.00–20.99	279	213	1.43	1.19, 1.72	1.42	1.15, 1.76	1.54	1.17, 2.03	1.54	1.22, 1.93
≥21.00	304	220	1.51	1.26, 1.81	1.34	1.09, 1.65	1.59	1.16, 2.18	1.59	1.22, 2.07
High/low exposure										
≤8.99	358	322	1.21	1.03, 1.43	1.12	0.96, 1.38	1.19	0.94, 1.51	1.19	0.99, 1.43
≥9.00	442	323	1.49	1.28, 1.74	1.39	1.16, 1.67	1.60	1.21, 2.12	1.59	1.28, 1.99
P value[g]			<0.0001		0.004		0.039		0.003	
P value[h]			0.01		0.61		0.40		0.24	

Abbreviations: CI, confidence interval; Cr(VI), hexavalent chromium; Ni, nickel; OR, odds ratio.

[a] Adjusted for log(age) and conditional on study.

[b] Additionally adjusted for log(pack-years + 1) and time since quitting smoking cigarettes (current smokers; ever other types of tobacco (pipes, cigars) only; stopped smoking 2–7, 8–15, 16–25, or ≥26 years before interview or diagnosis; never smokers).

[c] Additionally adjusted for ever working in at-risk jobs except in those with exposure to hot metal fumes and for average intensity of exposure to the other agents under study.

[d] Odds ratios for Cr(VI) and Ni (model 5) are additionally adjusted for ever working in at-risk jobs, except in those with exposure to hot metal fumes and for average intensity of exposure to welding fume.

[e] Subjects who were never exposed to metal fumes from welding or smelting.

[f] Cumulative exposure of single agents presented in $\mu g/m^3 \times$ years.

[g] *P* for trend values for log-transformed exposure variables.

[h] *P* for trend values for log-transformed exposure variables, tests restricted to exposed men.

for all agents, which might indicate that welding fumes, Cr (VI), and Ni contribute independently to the risk of developing lung cancer, given that we mutually adjusted for the other agents under study. We observed higher risks with increasing cumulative exposure levels but a weak trend for welding fumes only.

To our knowledge, this is the first compound analysis of these 3 agents using a measurement-calibrated WEM. Welding

Table 4. Joint Effects of the Lung Cancer Risks for Duration and Intensity of Exposure to Welding Fumes, Hexavalent Chromium, or Nickel in Men, Arbeit und Technik Study and Humanisierung des Arbeitslebens Study, Germany, 1988–1996

Cumulative Exposure	≤0.99 Years × Frequency				1.00–4.99 Years × Frequency				≥5.00 Years × Frequency[a]			
	No. of Cases	No. of Controls	OR[b]	95% CI	No. of Cases	No. of Controls	OR[b]	95% CI	No. of Cases	No. of Controls	OR[b]	95% CI
Reference group[c]	2,618	2,843	1.00	Referent	2,618	2,843	1.00	Referent	2,618	2,843	1.00	Referent
Welding fumes[d]												
≤1,799	173	176	0.98	0.64, 1.51	106	79	1.41	0.73, 2.75	98	65	2.27	1.18, 4.37
≥1,800	220	166	1.38	0.96, 1.99	88	61	1.42	0.86, 2.36	115	98	1.41	0.85, 2.32
Cr(VI)[d]												
≤0.99	89	66	0.78	0.41, 1.48	27	19	1.87	0.58, 6.02	36	27	3.49	1.24, 9.85
≥1.00	304	276	0.86	0.51, 1.45	167	121	1.75	0.72, 4.26	177	136	3.47	1.48, 8.12
Ni[d]												
≤5.99	114	90	0.77	0.43, 1.37	34	28	1.39	0.52, 3.72	45	31	3.53	1.41, 8.81
≥6.00	279	252	0.75	0.44, 1.27	160	112	1.50	0.65, 3.48	168	132	3.30	1.44, 7.56

Abbreviations: CI, confidence interval; Cr(VI), hexavalent chromium; Ni, nickel; OR, odds ratio.
[a] Median values were 10 years × frequency in cases and 11 years × frequency in controls.
[b] Adjusted for log(age), log(pack-years + 1), time since quitting smoking cigarettes (current smokers; ever other types of tobacco (pipes, cigars) only; stopped smoking 2–7, 8–15, 16–25, or ≥26 years before interview/diagnosis; never smokers), for ever working in a List A job except in those with exposure to hot metal fumes, and for average intensity of exposure to the other agents under study and conditional on study.
[c] Subjects who were never exposed to metal fumes from welding or smelting.
[d] Median shift concentration of single agents presented in $\mu g/m^3$.

fumes represent exposure to particulate matter, as well as to iron when welding steel (27). Higher mass concentrations of welding fumes are commonly emitted when welding mild steel, which has a lower Cr and Ni content than stainless steel, for example with gas metal arc welding (9). By contrast, stainless steel is frequently welded with low-emission techniques, such as tungsten inert gas welding. One challenge is the strong correlation of Ni with total Cr in welding fumes, which can be lower for Cr(VI) (28). Complex exposure scenarios, together with limitations of exposure assessment, might hinder the detection of dose-response relationships. Misclassification of exposure could be a reason for even higher risk estimates when mutually adjusting for the other agents under study.

The strengths of this study include a large number of exposed cases, a measurement-calibrated WEM, and adjustment for or stratification by smoking. Aside from the general limitations of the population-based case-control design with many "occasional" welders, the lack of individual and historical measurements can lead to misclassification when using job-exposure matrices (29, 30). In this study, welding was performed before the 1990s, whereas measurements were available only after the 1990s. Previous analyses revealed rather stable concentrations for each welding process across 3 decades (16–18), but improvements in fume extraction systems might have reduced exposure levels over time. Trends in using specific welding processes were captured in the welding histories.

Welding histories from the welding-specific questionnaire were linked with shift concentrations of a WEM, which was developed for European welders (13), and calibrated with large data sets of personal measurements (16–18). Various welding-specific challenges might cause misclassification and mask underlying dose-response relationships. Notably, more measurements were available for industrial processes, such as gas metal arc welding, than for occasionally applied techniques, such as autogenous welding.

The largest data set, with 15,473 measurements, was available for welding fumes (18). However, different samplers were used across time without side-by-side measurements. Because we cannot exclude a sampler effect, we estimated the lung cancer risk with and without the observed 3% reduction of the annual shift concentrations. Unknown factors, such as wearing a dust mask, could have influenced the concentration in the welders' breathing zone (9, 10, 28). Other uncertainties of the exposure assessment include the use of mass concentrations of inhalable welding fumes instead of the number of respirable particles. For example, tungsten inert gas welding generates many small particles at much lower mass concentrations than gas metal arc welding (9).

The assessment of metal exposure in welding fumes is even more challenging. Welders do not usually know the Ni content of consumable electrodes, which is a strong determinant of the shift concentration (17). Exposure databases can be biased towards higher concentrations when costly measurements, such as Cr(VI), are preferentially performed in settings with anticipated exposure (16). We therefore considered measurements when welding mild steel in this WEM (28). Another challenge is the skewed distribution of Cr(VI) concentrations, where the majority of measurements are below the limit of quantitation (16). Some individual welders might have been exposed to high concentrations (28), which cannot easily be captured at group level.

The job title "welder" and the years of welding are relatively robust data. An underreporting of occasional welding is possible, along with a potential misclassification of exposure time if

Table 5. Lung Cancer Risks in Relation to Cumulative Exposure to Welding Fumes, Hexavalent Chromium, or Nickel Stratified by Smoking in Men With Welding Activities, Arbeit und Technik Study and Humanisierung des Arbeitslebens Study, Germany, 1988–1996

Cumulative Exposure	Never Smokers				1.00–9.99 Pack-Years of Smoking			
	No. of Cases	No. of Controls	OR[a]	95% CI	No. of Cases	No. of Controls	OR[a]	95% CI
Reference group[b]	52	654	1.00	Referent	205	653	1.00	Referent
Welding fumes[c]								
≤1,837	6	61	1.57	0.41, 6.10	22	73	1.51	0.69, 3.32
≥1,838	7	68	1.59	0.39, 6.47	34	67	2.79	1.27, 6.13
P value[d]				0.448				
Cr(VI)[c]								
≤1.39	7	60	1.62	0.43, 6.12	22	79	1.87	0.72, 3.27
≥1.40	6	69	1.01	0.17, 6.00	34	61	4.48	1.84, 10.9
P value[d]				0.137				
Ni[c]								
≤8.99	7	59	1.20	0.40, 3.64	24	77	1.59	0.77, 3.27
≥9.00	6	70	0.66	0.16, 2.63	32	63	3.94	1.64, 9.44
P value[d]				0.314				
	10.00–34.99 Pack-Years of Smoking				≥35.00 Pack-Years of Smoking			
Reference group[b]	1,122	1,071	1.00	Referent	1,239	465	1.00	Referent
Welding fumes[c]								
≤1,837	172	129	1.15	0.79, 1.65	152	59	0.93	0.55, 1.56
≥1,838	211	131	1.36	0.93, 1.99	196	57	1.30	0.77, 2.19
Cr(VI)[c]								
≤1.39	159	124	1.17	0.82, 1.68	143	54	1.20	0.75, 1.92
≥1.40	224	136	1.64	1.07, 2.52	205	62	1.41	0.81, 2.45
Ni[c]								
≤8.99	184	143	1.34	0.97, 1.85	152	58	0.86	0.55, 1.36
≥9.00	226	141	1.65	1.13, 2.41	196	58	1.14	0.67, 1.93

Abbreviations: CI, confidence interval; Cr(VI), hexavalent chromium; Ni, nickel; OR, odds ratio.

[a] Odds ratios are adjusted for log(age), time since quitting smoking cigarettes (current smokers; ever other types of tobacco (pipes, cigars) only; stopped smoking 2–7, 8–15, 16–25, or ≥26 years before interview or diagnosis; never smokers), for ever working in at-risk jobs, except in those with exposure to hot metal fumes, and for average intensity of exposure to the other agents under study and conditional on study.

[b] Subjects who were never exposed to metal fumes from welding or smelting.

[c] Cumulative exposure of single agents presented in $\mu g/m^3 \times$ years.

[d] *P* values of multiplicative tests for interaction of each log-transformed exposure variable and log(pack-years + 1).

welding was not performed according to a regular schedule. Although we adjusted for working in occupations with recognized lung cancer risks, there could be confounding by other hazards.

Exposure to welding fumes in these community-based studies was lower than in industrial cohorts of welders due to the inclusion of occasional welders (12, 13, 15). Among the controls, our median concentration was 1.8 $mg/m^3 \times$ years, whereas the arithmetic mean for Danish mild-steel welders was 30.9 $mg/m^3 \times$ years (15). Besides lower exposure time, occasional welders usually do not apply high-emission industrial techniques. Autogenous welding was the most frequently reported welding process in our study. In the exposure database, 8,321 measurements were available for gas metal arc welding, but only 53 measurements for autogenous welding (18).

We observed higher risks with increasing duration and cumulative exposure for all agents under study but less clear results for the shape of dose-response relationships. Occasional welders have lower exposure levels than regular welders; however, they could be exposed to other carcinogens, which might add to the lung cancer risk of welding at low exposure levels. Also, healthy worker effects could influence the dose-response relationship, primarily at high exposure levels.

We used a cumulative exposure metric, which considers equitoxicity of concentration and duration of exposure. This might not fully reflect the mode of action of particulate matter, where defense mechanisms, such as alveolar macrophage-related clearance, with overload at high concentrations, have been discussed (31, 32). Less is known about the mode of action of both metals, where we observed a risk increase with duration of exposure.

We furthermore observed decreased risk estimates for "time since last exposure." These observations suggest that the cumulative exposure metric might be overly simplistic (22).

Interactions are difficult to interpret for the combinations of these 3 agents and for the association with smoking. Stratified risk estimates are based on smaller numbers (e.g., few never smokers among cases) and subject to variation by chance. Light smokers have a lower lung cancer incidence rate than heavy smokers (33). The highest welding-related risks were estimated among light smokers in this and other studies (4, 34). The additional cases caused by welding might contribute less to the relative lung cancer risks with increasing pack-years.

In conclusion, our findings support the classification of welding as carcinogenic to humans. Welding fumes, Cr(VI), and Ni might contribute independently to the elevated lung cancer risk in welders. Although we observed excess risks at higher exposure levels, limitations of the cumulative exposure metric together with welding-specific problems of the exposure assessment remain challenges in detecting dose-response relationships.

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