Eur J Epidemiol (2013) 28:159–168
DOI 10.1007/s10654-013-9784-0

CANCER

Diesel motor exhaust and lung cancer mortality: reanalysis of a cohort study in potash miners

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Received: 30 November 2011 / Accepted: 12 February 2013 / Published online: 19 February 2013

Abstract The aim of the reanalysis is to reassess lung cancer risk associated with occupational exposure to diesel motor exhaust in potash miners, while controlling for potential confounders such as smoking and previous occupational history. Our investigation is based on a cohort study of nearly 6,000 German potash miners, who were followed up from 1970 to 2001. The reanalysis also takes into account the employment periods before potash mining, in particular uranium mining. Different approaches (nested case–control study and Cox model) were used to adjust for confounding. The exposure estimates were recalculated, lagging the exposure by 5 years. Exposure groups were defined by tertiles of cumulative respirable elemental carbon (REC) exposure estimates and occupational categories, where exposure was estimated originally by representative measurements of total carbon for different occupations. The highest REC concentration was measured for production workers, about twice as much as for other occupations. The reanalysis revealed that while about 4 % of all study subjects had worked earlier in uranium mines, 10.3 % of later lung cancer cases did so. Although their absolute number was small, the corresponding relative risk estimator was significantly elevated. Our analysis did not show any notable association between cumulative REC exposure and lung cancer risk. Introducing cumulative REC exposure as a continuous variable into the conditional logistic regression model yielded an odds ratio of OR = 1.04 $[0.70\text{–}1.53]_{95\,\%}$ adjusted for smoking and previous employment. The study results give no evidence for an association between REC exposure and lung cancer risk. Only for very high cumulative dose, corresponding to at least 20 years of exposure in the production area, some weak hints for a possible risk increase could be detected. The study underlines the importance of assessing the entire occupational history in occupational studies, especially if the supposed dose–response-relationship is weak.

Keywords Lung cancer mortality · Diesel motor exhaust · Potash mining · Cohort study · Cox proportional hazard model

Introduction

For several decades, lung cancer has been the most common cancer in the world and the most common cause of death from cancer [1]. While smoking is the most important known risk factor for lung cancer, there are several other agents like arsenic, asbestos, nickel, radon or silica that have been classified as 'Carcinogenic to humans' by the International Agency for Research on Cancer (IARC). In addition, there are several agents where a carcinogenic risk could not yet be conclusively clarified. Until recently diesel motor exhaust (DME) belonged in the category IIa "probably carcinogenic to humans" [2], but in June 2012 an IARC working group came to the result that on the basis of recently published studies the evidence for DME can be upgraded, i.e. DME is now classified also as (group I) 'Carcinogenic to humans' by the IARC [3]. However, it should be noted, that the key studies for this decision [4–6] were published only very recently and, hence, they are still subject of scientific debate [7–9]. Exposure to diesel exhaust is virtually ubiquitous due to the wide range of industrial applications of diesel engines and their

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widespread use in cars and trucks, especially in urban regions. Therefore, large populations are exposed to diesel exhaust in their everyday life with a broad range of exposure intensity. The main criticism in previous evaluations of the carcinogenicity of DME has been that only very few studies are based on exposure measurements. As population-based case–control studies concerning DME are usually based on semi-quantitative exposure estimates only [10] cohort studies among highly exposed occupational groups with quantitative exposure estimates are needed to verify a potential exposure–response relationship. Reported DME-exposure levels are highest for underground mining [11]. However, exposure to DME in underground mining is usually closely linked with exposure to other lung carcinogens such as radon, arsenic or silica. Given that such concurrent occupational exposures to radon or silica are negligible in potash mines due to their geological characteristics, potash miners lend themselves to be a natural cohort to study the effect of DME exposure on lung cancer risk. The cohort study on lung cancer risk among workers at eight US non-metal mining facilities (DEMS study), which is one of the two key studies of the mentioned recent evaluation of DME by IARC, also includes three potash mines [4, 5]. In the following, we report about a reanalysis of data from a cohort of workers exposed to DME at six German potash mines.

In the beginning of the 1990s a cohort of about 6,000 potash miners in the south Harz Mountains region of Germany was recruited based on companies' medical records and a first analysis was conducted based on the follow-up from 1970 to 1994 [12]. Later on, the follow-up was extended until 2001 [13]. Both studies indicated a considerable, however not statistically significant risk. Because of sparse information on occupational history before entry into potash mining, the analyses did not take into account the miners' occupational history. The aim of the current study was to investigate the relationship between occupational exposure to DME and lung cancer mortality taking into account information on potential confounding factors, especially regarding possible former employment in mining before potash mining.

Methods

Study population

The potash mines in the south Harz Mountains region were reopened after World War II. To increase the productivity, mobile diesel powered vehicles were introduced in the potash production during 1969 replacing the electrically devices used before. The inclusion criterion for workers into the cohort was having been employed in the potash mines for at least 1 year after 1969. The ascertainment of information about the type of job in the mines was based on companies' medical records. As miners were subjected to preventive medical examinations every other year, their medical records also contained information about their workplace. Further details of the recruitment of the original cohort have been described elsewhere [12].

The basic cohort of the second follow-up comprised 5,862 miners. Persons with any implausible date specification were excluded from further analysis, decreasing the cohort to 5,819 individuals.

Exposure assessment

In 1991, exposure measurements of the concentration of total carbon (TC) in the airborne fine dust fraction by coulometric analysis were undertaken. Details of the measurement procedure are described in detail elsewhere [14]. To a lesser extent, also measurements of elemental carbon (EC) were available. As the mining technology and the mining equipment remained fairly stable since 1969, measurements from 1991 have been used for designing a job-exposure-matrix (JEM) with three main job categories: production, maintenance, and workshop, corresponding to an estimated exposure concentration of 0.244, 0.144, and 0.120 mg/m^3 TC respectively [12]. EC was the largest component of TC with a proportion of weight of about 63 %. Moreover, the two measures were highly correlated ($r = 0.894$) [14]. Therefore, we converted the JEM now to respirable elemental carbon (REC), to allow a better comparison with the results of other recent studies.

The job history of each miner was compiled from the medical records on an annual basis. As in previous analyses, we used cumulative exposure as the exposure measure albeit with the modification, that in accordance with other cohort studies in miners, the cumulative exposure was calculated, taking into account a 5 year exposure lag, i.e. the lagged cumulative exposure for a certain year being equal to the cumulative exposure 5 years earlier [15, 16].

In the first half of the 1990s the potash mines were consecutively closed, leading to a stepwise employee layoff peaking in 1991. Therefore, the duration of exposure to DME was restricted to 22 years for most of the miners.

Mortality follow-up

The vital status for cohort members was ascertained until 2001, i.e. for most study subjects this information is available for at least 10 years after the last exposure [13]. In previous analyses a death was classified as a lung cancer death only, if lung cancer was specified as the underlying cause of death on the death certificate. For the present internal analysis, all death certificates were reviewed again to identify all those cases in addition, for which a primary lung cancer (ICD9: 162; ICD10: C34) was noted on the death certificate as a contributing cause of death.

Information about other lung cancer risk factors

As smoking is the most important risk factor for lung cancer, smoking status should be considered as a potential confounding factor. Information on the smoking status of potash miners was collected from the medical records. Reviewing the original cohort data it became obvious that the availability of information on smoking status—and also on occupational history before potash mining—was strongly related to the miners' year of birth (Table 1). Moreover, a strong correlation between year of birth and mean age at hire was observed. Hence, it should be considered that miners born before 1940 could have been exposed to occupational lung carcinogens during previous jobs without this information being available.

The steepest increase of the workforce in the potash mines was observed in the mid 1950s. During the same period, the workforce of the uranium mining company "WISMUT" was markedly reduced—by 50,000 in 5 years [17]. Assuming that some miners switched from uranium to potash mining a record linkage between the cohort and the data from the occupational health data archives of former WISMUT miners, which is operated by the Federal Institute for Occupational Safety and Health, was performed.

Statistical methods

As shown in the descriptive analysis (Table 2), year of birth was strongly related to the outcome. Therefore, it was decided to conduct the analysis as a matched case–control study nested into the cohort. Five controls were matched to each lung cancer case, i.e. those five controls whose date of birth was closest to that of the case were selected.

The dose–response analysis was based on a conditional logistic regression model, assuming either a linear dose–response relationship or based on percentiles of cumulative REC exposure. To take into account the exposure lag under the case–control study design also for controls, the cumulative exposure for those individuals was calculated until the date when the control reached the age of the corresponding cases' death less the assumed lag time (5 years).

The mean REC intensity for the three job groups does of course not consider either the intra-job variability or the variability over time of the exposure. Nevertheless, it is indubitable that the REC exposure was by far the highest in the job category 'production'. The estimated REC concentration there was nearly twice as high as in other jobs. To validate the results of the analysis based on cumulative REC exposure, all study subjects were allocated into subgroups according to the job they held at entry into the study. The categories 'maintenance' and 'workshop' were collapsed into one category, because their exposure intensity was very similar.

Table 1 Availability of information about smoking status, former employment, age, and year of hire by year of birth in the potash miner cohort

Year of birth	N	Availability of smoking status (%)	Availability of information about former employment (%)	Mean age at hire	Mean year of hire
<1920	138	3.6	23.9	39.3	1954
1920–1929	530	41.5	40.0	29.3	1955
1930–1939	1,457	79.0	55.3	23.3	1958
1940–1949	1,310	86.9	71.8	20.9	1965
1950–1959	1,270	83.7	74.4	20.3	1975
≥1960	1,114	95.4	84.6	18.3	1983
Total	5,819	79.8	66.7	22.1	1968

Table 2 Mean cumulative REC exposure, proportion of miners with a history in uranium mining, and distribution of lung cancer cases by year of birth in the potash miner cohort

Year of birth	N	Mean cumulative REC exposure ($\mu g/m^3$-year)	Proportion of miners with a history in uranium mining (%)	Number of lung cancer cases
<1920	138	672	7.3	6
1920–1929	530	1,302	6.0	30
1930–1939	1,457	1,838	5.8	28
1940–1949	1,310	1,957	4.4	4
1950–1959	1,270	1,459	2.6	0
≥1960	1,114	800	1.3	0
Total	5,819	1,507	4.0	68

Smoking status and previous occupational history in mining other than potash mining or in heavy industries were considered as potential confounding factors. Information about smoking habits was given in the medical records in categorical form: never smoker, occasional smoker (≤5 cigarettes/day), former smoker, and current smoker (>5 cigarettes/day). The percentage of occasional smoker was negligibly small and for former smoker it was not clear at which time they stopped smoking. Therefore, we used for our analysis only a rough classification into never smoker and ever smoker. Information about previous employment was also given in few categories: no former employment, heavy industry/mining, agriculture, building industry, other branches, and various branches. In view of the fact that also other mines were located not very far away from the potash mines (especially copper slate mines and uranium mines) our focus was on heavy industry/mining. The other groups were dominated in terms of frequency by "other branches". Hence, we collapsed all non-mining categories into one. Based on the results of the record linkage with the occupational health data archives of former WISMUT miners the final categorisation was defined: no employment in mining or heavy industries, uranium mining, other mining or heavy industry, no employment in uranium mines but missing further information.

To verify the results of the nested case–control approach, the same variables were introduced into a Cox model for the full cohort. Such models have been used also in the preceding analysis of this cohort, with different time axes and, hence, different results [13]. The recommendation for the Cox models is to use age as the time variable in cohort studies because incidence and mortality rates rise rapidly with age and age effects should be controlled as precisely as possible in cohort studies [18, 19]. This recommendation is also supported by corresponding simulation studies [20]. It should be noted, that in contrast to the preceding analysis, we introduced cumulative exposure into proportional hazard models as a time-dependent variable—again taking into account an exposure lag of 5 years.

We also investigated whether the results of the internal analysis corresponded with those for an external analysis using appropriate reference rates. Unfortunately, regional age specific lung cancer mortality rates were not available. Therefore, we used for the calculation of standardized mortality ratios (SMR) the annual rates for the area of the former East Germany, available for 5-year age groups. But the data of the East German cancer atlas [21] show clearly, that the total lung cancer incidence in the south Harz Mountains region is significantly lower than for the whole catchment area of the cancer registry. In the 1980s the mean standardized incidence ratio for those counties, where the potash mines where located, was about 0.73. Assuming that the mortality rates will be lower in the same order of magnitude in our study region, we multiplied reference rates by this factor to adjust for regional deviation in lung cancer mortality.

All statistical analyses have been executed with the software package STATA® release 12 [22].

Results

The re-survey of the death certificates showed that among the deceased miners a total of 68 primary lung cancer cases appeared. Seven of these cases (10.3 %) were also identified as former employees in the uranium mines. The complete linkage of the cohort with the occupational health data archives of former WISMUT miners revealed that 232 miners (4 %) were engaged in uranium mining before hired in potash mines.

Miners, who died of lung cancer and their age-matched controls had worked on average already more than 13 years in the potash mines before the diesel technology was introduced. At the time of the technology change they were already more than 40 years old (Table 3). The combination of the information from the medical records and the record linkage showed that among the lung cancer cases at least 19 % had worked before in other mining or heavy industry jobs (Table 4).

The conditional logistic regression models did not show any notable association between cumulative REC exposure and lung cancer risk neither with the use of categorized exposure data (tertiles; Table 5) nor under the assumption

Table 3 Description of main characteristics of lung cancer cases and controls (mean values and ranges or percentages)

	Cases	Controls
N	68	340
Year of birth	1929 [1913–1946]	1929 [1913–1946]
Age at hire (years)	27.6 [14.0–49.5]	27.5 [14.0–51.4]
Age at exposure start (years)	41.3 [25.4–56.6]	41.3 [24.1–59.4]
Cumulative REC exposure (μg/m^3-years)	1,436 [302–3,226]	1,468 [0–3,383]
Smoking status unknown (%)	52.9	45.3
Ever smoker (among known status) (%)	90.6	51.1
Missing information about occupational history from medical records (%)	63.2	54.4
Information about former employment in mining or heavy industries (among known status) (%)	32.0	16.1

Table 4 Information about jobs held prior to potash mining

Jobs held prior to potash mining	Lung cancer cases			Controls		
	N	%	Mean age at hire	N	%	Mean age at hire
No employment in mining or heavy industries	16	23.5	22.1	121	35.6	23.5
Employment in uranium mining	7	10.3	32.8	20	5.9	28.3
Employment in other mining or heavy industries	6	8.8	34.8	23	6.8	32.2
No employment in uranium mining, but missing information on other employment outside potash mining	39	57.4	27.8	176	51.7	29.5
Total	68	100.0	100.0	340	100.0	100.0

Table 5 Results of the conditional logistic regression models for cumulative REC exposure subdivided into tertiles

	Without adjustment		With adjustment	
	OR	95 % CI	OR	95 % CI
Cumulative REC exposure				
1st tertile (<983 μg/m^3-year) [mean = 624 μg/m^3-years]—reference	1.00	–	1.00	
2nd tertile (983–1,550 μg/m^3-years) [mean = 1,279 μg/m^3-years]	1.48	0.74–2.94	1.77	0.85–3.69
3rd tertile (>1,550 μg/m^3-years) [mean = 2,375 μg/m^3-years]	0.86	0.40–1.82	1.04	0.47–2.27
Smoking status				
Never-smoker—reference			1.00	–
Ever-smoker			9.42	2.76–32.19
Smoking status unknown			8.34	2.25–30.95
Jobs held prior to potash mining				
No employment in mining or heavy industries—reference			1.00	–
Employment in uranium mining			3.65	1.20–11.14
Employment in other mining or heavy industries			2.12	0.69–6.46
No employment in uranium mining, but missing information on other employment outside potash mining			1.75	0.88–3.50

of a linear exposure–response relationship (Table 6). As expected, smoking was identified as the main risk factor in the analysis even though the information on smoking status was very rough. Moreover, the analysis showed clearly that previous employment in industries characterized by a high probability of exposure to lung carcinogens contributed to the lung cancer risk of potash miners. Although the number of lung cancer cases with a history of uranium mining was small, the corresponding odds ratio was significantly elevated (OR = 3.65 $[1.20–11.14]_{95\ \%}$ in the model with tertiles of cumulative REC exposure). It should be noted that the mean age of hire at the potash mines for lung cancer cases was more than 10 years higher for those with a former employment in mining or heavy industry in comparison with those without such an occupational history (Table 4).

The comparison of the two job groups yielded a lower risk estimate for production workers (OR = 0.80 $[0.46–1.40]_{95\ \%}$), but their cumulative REC exposure was considerably higher (1.84 vs. 1.01 mg/m^3-years).

The estimates resulting from the Cox model differed only marginally from those derived from the nested case–control approach (Table 7). This is also valid for estimates of the other model parameters concerning smoking and occupational history. Moreover, the comparison of the two job categories yielded a similar result as the case–control approach (HRR = 0.93 $[0.58–1.50]_{95\ \%}$).

The comparison of the SMR for lung cancer confirms the effect of previous occupations on the lung cancer risk reported from the internal analysis (Table 8). Moreover, it turned out that miners without a history in other mining had had the highest cumulative REC exposure on average but the lowest lung cancer SMR. Miners from the production area had had a substantially higher cumulative REC exposure, but their SMR was only a little higher than that for maintenance/workshop.

Discussion

Our case–control study nested within a cohort of six potash mines did not show a relationship between exposure to diesel motor exhaust and lung cancer risk. But it clearly demonstrated that previous occupational exposures had an impact on the lung cancer risk that was not negligible.

To evaluate the influence of the choice of the lag time, the analysis of the nested case–control study was repeated using different lag times (1, 5, 10, 15, 20, and 25 years) and different subdivisions of the cumulative REC exposure (tertile, quartile, quintile, sextile) as well as a linear relationship. In addition to the model without any adjustment we considered a model with adjustment for smoking only as well as for smoking and occupational history. Moreover, the corresponding models without exposure to DME were compared. We used Akaike's information criterion to compare the goodness of fit in due consideration of different number of model parameters [23]. It turned out, that the model with smoking as independent variable only yielded the best fit. In view of the clear effect of former uranium mining on the lung cancer risk we repeated the model comparison excluding all miners with a history in uranium mining. Applying this restriction the model based on quintiles of cumulative REC exposure, lagged 10 years, and adjusted for smoking yielded the best fit. But the corresponding parameter estimates did not really suggest a dose–response relationship (the corresponding odds ratios for the five quintiles in increasing order were estimated to be 1.00 for the reference category, 0.46, 1.72, 0.40, and 0.76).

In the previous analyses some elevated risk estimators were derived for very highly exposed miners [13]. Therefore, comparing highly DME exposed versus lower DME exposed miners under the case–control approach and

Table 6 Results of the conditional logistic regression models for cumulative REC exposure assuming a (log-)linear dose–response relationship

	Without adjustment		With adjustment	
	OR	95 % CI	OR	95 % CI
Cumulative REC exposure (per 1 mg/m^3-year)	0.94	0.64–1.38	1.04	0.70–1.53
Smoking status				
Never-smoker—reference			1.00	–
Ever-smoker			9.39	2.76–31.93
Smoking status unknown			8.49	2.30–31.33
Jobs held prior to potash mining				
No employment in mining or heavy industries—reference			1.00	–
Employment in uranium mining			3.25	1.09–9.73
Employment in other mining or heavy industries			1.99	0.66–5.98
No employment in uranium mining, but missing information on other employment outside potash mining			1.69	0.85–3.34

Table 7 Comparison of two approaches for estimating relative risk estimates for REC exposure parameters with different models

	Nested case–control approach		Cox model for the full cohort	
	OR	95 % CI	HRR	95 % CI
REC (continuous, per 1 mg/m^3-year)	0.94	0.64–1.38	1.00	0.75–1.33
REC (continuous), adjusted for smoking and occupational history	1.04	0.70–1.53	1.16	0.85–1.58
REC 2nd tertile versus 1st	1.48	0.74–2.94	1.37	0.76–2.47
REC 3rd tertile versus 1st	0.86	0.40–1.82	0.82	0.45–1.50
REC 2nd tertile versus 1st, adjusted for smoking and occupational history	1.77	0.85–3.69	1.74	0.95–3.18
REC 3rd tertile versus 1st, adjusted for smoking and occupational history	1.04	0.47–2.27	1.06	0.56–2.02
REC 2nd quartile versus 1st	0.82	0.38–1.76	0.77	0.39–1.51
REC 3rd quartile versus 1st	0.99	0.43–2.29	0.85	0.43–1.66
REC 4th quartile versus 1st	0.66	0.28–1.57	0.78	0.39–1.53
REC 2nd quartile versus 1st, adjusted for smoking and occupational history	0.90	0.41–1.95	0.92	0.46–1.82
REC 3rd quartile versus 1st, adjusted for smoking and occupational history	1.16	0.48–2.80	1.15	0.56–2.36
REC 4th quartile versus 1st, adjusted for smoking and occupational history	0.78	0.32–1.91	1.06	0.50–2.23

Table 8 SMR for lung cancer in potash miners by different subgroups (restricted to miners born before 1950)

Subgroup definition/category	Mean exposure (μg/m^3-years)	Mean year of birth	Proportion of ever smoker (%)	Observed cases	Expected cases	SMR	95 % CI
Smoking status							
Never smoker	1,934	1938	0	2	20.53	0.10	0.01–0.35
Ever smoker	1,997	1938	100	28	21.77	1.29	0.85–1.86
Status unknown	1,166	1930	–	31	26.84	1.16	0.78–1.64
Total	1,751	1936	51.9	61	69.13	0.88	0.67–1.13
Employment in mining or heavy industry before potash mining							
Not such an employment	1,934	1938	49.6	13	25.53	0.51	0.27–0.87
Uranium mining	1,695	1935	52.6	6	4.13	1.45	0.53–3.16
Other mining or heavy industry	1,720	1936	49.8	5	6.17	0.81	0.26–1.89
Not stated, but definitely not in uranium mining	1,575	1934	56.6	37	33.29	1.11	0.78–1.53
Total	1,751	1936	51.9	61	69.13	0.88	0.67–1.13
Type of job at study entry (uranium miners excluded)							
Maintenance/workshop	1,310	1936	48.0	25	32.13	0.78	0.50–1.15
Production	2,199	1936	55.8	30	32.86	0.91	0.62–1.30

Table 9 Relative lung cancer risk estimates for very high exposed versus lower exposed miners, based on dichotomized cumulative REC exposure (lagged 5 years) with different cut-off points (without former uranium miners)

Cut-off point (mg/m^3-years)	Mean exposure above/below cut-off point (mg/m^3-years)	Number of highly exposed cases/controls	Without adjustment		Adjusted for smoking	
			OR	95 %-CI	OR	95 %-CI
2.5	2.89/1.20	11/51	1.01	0.46–2.20	1.04	0.47–2.34
2.6	2.93/1.23	11/45	1.21	0.55–2.69	1.20	0.53–2.71
2.7	2.98/1.26	10/38	1.32	0.58–2.98	1.27	0.55–2.95
2.8	3.04/1.31	8/30	1.34	0.54–3.36	1.31	0.51–3.40
2.9	3.09/1.35	7/23	1.51	0.58–3.92	1.61	0.57–4.52
3.0	3.17/1.40	5/14	1.79	0.58–5.55	1.67	0.51–5.51

shifting the cut-off point upwards, always produced a number of exposed cases not less than five. From a cumulative REC exposure of 2.6 mg/m^3-years the odds ratio increased, however, the number of exposed cases and controls was small and, hence, the statistical precision of those estimates was rather low (Table 9). Furthermore, it should be stressed that REC exposure intensity for the production worker in our study is about 50-fold as high as exposure intensity of surface-only worker in the recent study in US non-metal mining facilities [4].

To validate our results, all analyses have been repeated using corresponding proportional hazard models. The risk estimators resulting from these models differed only marginally from that of the nested case–control approach. In view of the discussion about the choice of the most appropriate time axis, we compared the models with different time axis in our data in terms of Akaike's information criterion [23]. It turned out, that models with age as the time variable yielded a considerably better fit to the data (data not shown). Hence, only age should be used as the time variable in the analysis of the potash miner cohort.

The SMR analysis emphasized the effect of concurrent lung cancer risk factors. The highest SMR was observed for former uranium miners, followed by individuals without any information about previous employment from the medical records. Taking into account the year of birth and the year of hire at the potash mines, it is well possible that some of the miners without information about previous employment from the medical records have worked for a considerable time as prisoners of war for example in Soviet coal mines. Interpreting the difference in risk between the two job groups in terms of SMR also the difference in smoking habits should be taken into account. Additionally, we compared the SMR by tertiles of cumulative REC exposure (Table 10). It should be noted, that those individuals adding person-years to the highest tertile belonged to the production group without exception. Therefore, the small difference in the SMR might well be attributed to the difference in smoking patterns. But also differences in previous occupational exposures could not be ruled out. To exclude a possible impact of former employment, we separately investigated the small group of miners where

Table 10 SMR for lung cancer in potash miners by tertiles of cumulative REC exposure (restricted to miners born before 1950)

Cumulative REC exposure (μg/m^3-year)	Mean exposure (μg/m^3-year)	Person-years	Observed cases	Expected cases	SMR	95 %-CI
All but former uranium miners						
<1,076	416	55,084	20	28.11	0.71	0.43–1.10
1,076–1,691	1,386	19,501	17	18.11	0.94	0.55–1.50
≥1,691	2,413	18,655	18	18.78	0.96	0.57–1.51
Only miners without previous employment in mining or heavy industries						
<1,512	617	32,598	7	14.22	0.49	0.20–1.01
≥1,512	2,274	12,980	6	11.32	0.53	0.19–1.15

Table 11 Characteristics of the two occupational subgroups, born before 1950 only (mean values)

Job held at study entry	Production	Maintenance/ workshop
N	1,731	1,704
Year of birth	1936	1936
Year of hire	1959	1961
Age at hire (years)	23.2	24.7
Duration of exposure (years)	15.6	16.2
Length of follow-up (years)	28.8	28.3
Time since hire (years)	39.9	38.3
Cumulative REC exposure (μg/m^3-years)	2,192	1,304
Employed before in uranium mining (%)	5.8	5.0
Proportion of ever smoker, if status is known (%)	55.8	48.0

such an employment could virtually be excluded. This group was divided into two groups only, to avoid to small numbers. This comparison yielded nearly equal SMRs, even if the mean cumulative REC exposure differed by a factor of more than three between both groups (Table 10).

Lung cancer deaths occurred in the miners' cohort only among those born before 1950. Considering this and the non-linear relationship between year of birth and cumulative REC exposure in our cohort, we restricted the SMR analysis to those individuals born before 1950. Miners from the production group as well as from maintenance/workshop had spent on average more than 25 years in the potash mines, among them more than 15 years after dieselization (Table 11). Of course, as in most occupational studies a healthy worker effect (HWE) must be taken into consideration. But it is well known that the strength of the HWE tends to diminish with increasing time since first employment [24]. For the relevant birth cohort in our study the time elapsed between the year of hire and the first exposure to DME is on average already about 10 years (Table 11). Taking into account, that more than 85 % of lung cancer deaths were reported only after 1985, the HWE might be rather low.

Former uranium miners were 5 years older when hired, compared to other lung cancer cases. Moreover, all but one miner were born in the 1920s. Therefore, they could have been engaged in uranium mining for even more than 10 years with high exposure levels of radon and respirable quartz dust. Often those miners retire at an age less than 60 years, due to serious health problems. Consequently, their cumulative REC exposure was lower (mean value = 1,065 μg/m^3-years) in comparison to other lung cancer cases (Table 3). On the contrary, in miners not deceased from lung cancer, only negligible differences are seen in main characteristics with regard to former uranium mining.

The JEM used in our study is based on a set of 255 concentration measurements for TC performed in 1991 covering all workplaces in the mines. We transformed TC into REC for our analysis, knowing that the two measures were highly correlated. This transformation might have slightly increased the random errors in the results. We cannot exclude the possibility of exposure misclassification to a certain degree. Especially miners from the maintenance group might have been exposed by varying REC exposure at different workplaces. But there is no doubt that production worker have had on average the highest exposure in all mines.

The number of lung cancer cases in our study which could possibly be attributed to DME is only 61. Therefore, the corresponding confidence intervals are wide and the precision of the point estimators is low. On the other side, only the DEMS study had comparably high exposure intensity such as in our study was observed and the number of cases was twice as much as in ours.

The synopsis of our results gives no evidence for an association between cumulative REC exposure and lung cancer risk. Only for a very high cumulative REC exposure, corresponding to at least 20 years of exposure in the production area, some weak hints for a possible risk increase could be detected. Under all model assumptions considered, previous employment in uranium mines was consistently recognized as a significant risk factor for lung cancer mortality. The fact that the occupational exposure in uranium mines, especially to radon, is connected with an increased lung cancer risk has been known for a few decades. Details of the exposure–response-relationship between exposure to ionising radiation and lung cancer risk have been investigated on a large-scale cohort study in Wismut uranium miners [15, 25, 26]. Nevertheless, it is astonishing that the relationship between uranium mining and lung cancer was detected with statistical significance in our study even though the number of lung cancer cases with such an occupational history was very small. This can be interpreted as a hint to the fact that the risk referring to DME is at least much smaller, than the risk linked with radon. Bergdahl et al. [16] achieved a similar result in their cohort study among Swedish ore miners. Radon and crystalline silica turned out to be the dominant occupational risk factors for lung cancer. DME did not play any role in the multifactorial analysis. Furthermore, in a large study on coalminers adjusted for age and smoking habits no evidence of an increase in lung cancer mortality with duration of DME exposure or cumulative DME exposure was found [27, 28]. Limited evidence of an association between lung cancer mortality and cumulative diesel exhaust exposure was detected for only one single colliery, but any suggestion of a relationship between lung cancer death and DME are explainable by different environmental conditions, especially dust concentrations, among the ten collieries investigated.

The largest database for the analysis of the relationship between exposure to DME and lung cancer until now is the DEMS study [4, 5]. The SMR for lung cancer was moderately but significantly elevated (1.21 for ever-underground workers and 1.33 for surface-only workers). The a priori defined analyses did not reveal a relationship between REC exposure and lung cancer risk. Only after stratification by worker location a strong relationship was detected leading to relative risk estimators of about 5 for the highest exposure category. However, it should be noted that the mean underground tenure in that cohort was only 8 years. In our cohort, by contrast, the mean underground tenure was 20 years. Therefore, occupational exposures before or after the employment under consideration might have affected the results in the DEMS study, even stronger than in our study.

Moreover, the simultaneous adjustment for smoking and worker location, which requires the estimation of additional 15 parameters, seems to influence the risk estimators markedly. The reported results indicate that compared to surface-only worker the ever-underground worker smoke significantly more, have a higher exposure to DME and to other occupational lung cancer risk factors, taking the SMR for pneumoconiosis as an indicator. Therefore, those findings are in some contrast to the reported lower lung cancer SMR for ever-underground worker.

Outside the mining industry a large cohort study was conducted in the US trucking industry [6, 29]. Among 31,135 male employees of four national trucking companies $\geq$40 years of age 779 lung cancer death were recorded from 1985 through 2000. The authors reported an elevated relative lung cancer risk (HR $= 1.09$ $[0.99\text{–}1.20]_{95\,\%}$ per mg/m^3-month), assuming a 10-year exposure lag and adjusting among other factors for duration of employment. But only with adjustment for duration of work a dose–response relationship could be shown, and the analysis by average exposure failed to show any association with lung cancer risk. The reported SMR for lung cancer among drivers in this occupational cohort are slightly elevated (SMR $= 1.10$ $[1.02\text{–}1.19]_{95\,\%}$) [30], i.e. similar to the risk estimates derived from the pooled population-based case–control study [10, 31, 32]. Interpreting those results, it should be taken into consideration that especially in long-haul drivers also other risk factors such as non-regular shift-work, sleep deprivation, sedentary lifestyle, unhealthy diet and environmental tobacco smoke may have an impact on the lung cancer risk [33].

Finally, we conclude that results from our study do not show an association between exposure to DME and lung cancer risk. But it underlines the importance of assessing the entire occupational history, especially if the supposed dose–response-relationship is weak. Other recent studies reported slightly to moderately elevated risk estimates, but the effect of concurrent risk factors could not be ruled out sufficiently. Even if the IARC has recently classified DME as a group I carcinogen, further research will be useful, to specify our present knowledge about the corresponding dose–response relationship and the interactions with concurrent lung cancer risk factors.

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