Lung cancer mortality and carbon black exposure – A nested case-control study at a German carbon black production plant

Introductory note
A portion of this article, including further details on, e.g., re-collection of job histories, obtained carbon black exposure estimates, tobacco consumption, external exposures, and a more detailed discussion of different aspects is published online only. To assist the reader we repeated the organisation and some parts of the text as published in-print.

Methods
Re-collection of data on job histories
In order to introduce a quality check of the data on job histories we re-collected all information on job histories for all members of study group 1 (blinded to case-control status). The data were extracted from personnel files which were kept at the carbon black plant. All documents in the files which held any information on the performed job at a certain time or in general were considered in the data re-collection step. The data were structured in such a way that we could assign a job history comprising at least one job phase to each subject. A job phase consisted of a beginning date, an ending date, and - where available - of a description of the performed job. The next step was to assign job titles according to the JEM (Job Exposure Matrix) which was established by Wellmann et al. 2006\(^1\) and described in its improved version in Morfeld et al. 2006\(^2\). Finally, we compared each subject’s re-collected job history data with the data originally gathered by Wellmann et al. 2006\(^1\). In case of discrepancies we again looked up the paper files and worked out a solution approved by the complete study team.

Carbon black exposure estimates
Based on the job histories we determined for each subject of study group 1 whether he had ever worked in the lamp black, gas black, and furnace black plant (sub-)section (blinded to case-control status). We also computed the cumulated years worked in each of these three departments and whether a subject was actively working in one of the three departments at the time of death of the case. For the analyses these estimates were
calculated applying a lag of 0, 5, 10, 15, and 20 yrs (years). The chosen plant (sub-)sections were also used in the analyses as presented in Morfeld et al. 2006².

We applied the improved JEM (Morfeld et al. 2006²) to the job information for all study members. All missing data were treated as described in Morfeld et al. 2006² and we estimated the carbon black exposure for each subject based on the four exposure models also described in this publication (exposure models A, B, C, and D).

Thus, four different approaches were chosen to assess exposure in our analyses:

A) JEM as applied by Wellmann et al. 2006¹
B) JEM A) but modified to include the stepwise development in some jobs as well as the corrections suggested by the experts
C) JEM B) but time-dependent imputation of mean values for the missing data
D) JEM C) but considering no constant exposure intensity before 1960.

Furthermore, we separated cumulative carbon black exposure into mean exposure, instantaneous (at a particular time) exposure and duration of exposure. The exposure estimates were calculated for controls and cases at the time of death of the case in the respective stratum and lagged for 0, 5, 10, 15, and 20 yrs. For a rationale of this approach see Morfeld et al. 2006². Cumulative exposure to Carbon Black was calculated in terms of Carbon Black score units (u) multiplied by years of work (yrs), i.e., in the unit u-yrs.

Re-collection of smoking information from occupational medical files

Results on the impact of smoking indicated an underestimation of lung cancer risk related to smoking in the cohort analyses (Morfeld et al. 2006³). Thus, we recollected all available information on smoking behaviour from the occupational medical files for all study group members (blinded to case-control status). Such information was starting and quitting date of smoking as well as smoking intensity in terms of cigarettes, cigarillos, and pipes smoked per day. Subjects with missing data on starting smoking were considered to have started on their 21st birthday (mean age of starting smoking among smokers with information available), subjects with missing data on when they quit smoking were assumed to have smoked until they left the study. In case the smoking intensity was undefined we assumed the intensity to be 20 cigarettes a day. The consumption of cigarillos and pipes was
converted into equivalent amounts of cigarettes (Boffetta et al. 1999\textsuperscript{3}, Boffetta et al. 1999\textsuperscript{4}). We considered a subject's smoking behaviour to remain unchanged until a change was documented in the medical files. We calculated cumulative tobacco consumption in terms of pack-years, one pack-year corresponding to 20 cigarettes smoked per day over one year.

\textit{Asbestos exposure and contact to feedstock oil at the carbon black plant}

Morfeld et al. 2006\textsuperscript{2} suggested that subjects might have been co-exposed to asbestos dust during their employment at the carbon black plant. We therefore estimated retrospectively for each subject of study group 1 his exposure to asbestos dust by consulting with senior occupational safety plant staff. Experts were blinded to case-control status. The asbestos dust exposure was time-dependently estimated on a four level scale (no exposure=0, low exposure=1, moderate exposure=2, high exposure=3) for each individual on the basis of the information on performed jobs provided by the job histories. We computed for each subject his time-dependent cumulative exposure to asbestos dust in terms of ‘asbestos exposure level’ (in units asb) times ‘duration of exposure’ (in years), i.e., measured in asb-yrs. The calculation was performed applying a lag of 0, 5, 10, 15, and 20 yrs. In addition, the cumulative duration of exposure was calculated, also lagged by 0, 5, 10, 15, and 20 yrs. Furthermore, we created a time-dependent indicator variable informing on whether a subject was ever exposed to asbestos, and time-dependent indicator variables whether a subject had ever received low, moderate, or high exposure to asbestos dust (again applying a lag of 0, 5, 10, 15, and 20 yrs).

\textit{Contact to feedstock oil at the carbon black plant}

In addition to asbestos dust as a potential co-exposure Morfeld et al. 2006\textsuperscript{2} hypothesized that subjects might have received exposure to polycyclic aromatic hydrocarbons (PAH) due to contact to feedstock oil during their work, in particular in specific plant sections or sub-sections. We consulted with senior plant staff and a former plant general manager to identify jobs that incorporated contact to feedstock oil. The experts rated each job carried out by study group 1 members in different time periods whether feedstock contact was likely or unlikely on a two level scale (0/1). Experts were blinded to case-control status. We created a time-dependent indicator variable informing on whether a subject ever had
contact with feedstock oil, and a variable holding the cumulative years worked with contact to feedstock oil.

External occupational exposures

Since one supposed possible explanation for the increased lung cancer SMR (Wellmann et al. 2006\textsuperscript{1}) was, that subjects might have already been under an increased risk of dying of lung cancer before they started their employment at the carbon black plant (Morfeld et al. 2006\textsuperscript{2}), we combined the job history assessment process described above with a screening of the personnel files for documents that provided information on jobs performed externally by members of study group 1 mainly prior to their hiring at the carbon black plant. Such documents were e.g. entry forms filled out by the employee during the hiring process or documents handed over to the carbon black plant by subjects’ former employers. Due to the possibility that subjects might have left the plant, worked somewhere else, and then re-entered the plant, we also gathered available information on these intermediate external employments. We conducted extensive data checks to eliminate inconsistencies. If information on prior or intermediate employments was too unspecific we consulted with senior staff from the carbon black plant who themselves performed further research work to provide for more detail on the nature of the external employment. All work was performed blinded to case-control status.

We took two approaches to assign to each external job an estimate for exposure to lung carcinogens: an automatic approach based on the CAREX system (Kauppinen et al. 2000\textsuperscript{5}) and an independent approach by expert rating.

The CAREX approach: automatic assessment of lung carcinogen exposure

Blinded to case-control status we categorized each job in study group 1 according to the United Nations’ international standard industrial classification (ISIC 2005\textsuperscript{6}) revision 2 (1968) as used in Table 2 of Kauppinen et al. 2000\textsuperscript{5}. Based on this categorization the CAREX system (Kauppinen et al. 1998\textsuperscript{7}, CAREX 2005\textsuperscript{8}) can be automatically applied to estimate industry specific information on the proportion of the workforce exposed to a number of carcinogenic agents. A list of expected occupational lung carcinogens weighted
by probability of occurrence was published in Table 4 by Driscoll et al. 2004\(^9\) using broad CAREX categories: crystalline silica, cadmium, nickel, arsenic, chromium, diesel fumes, beryllium, and asbestos. We used this information and derived a time-dependent indicator variable for exposure to each of these eight agents. The indicator was set to ‘one’ for those subjects that had worked in an industry sector of which the workforce proportion exposed to one of the agents was greater than the proportion in at least 75% of all other industry sectors. Variables that refer to the CAREX data were additionally labelled with ‘CAREX’ in parentheses.

**The expert approach: rated assessment of lung carcinogen exposure**

The other approach was the involvement of an external German expert (U. B.-A.) who has participated in a large German lung cancer case-control study (Jöckel et al. 1998\(^{10}\), Brüske-Hohlfeld et al. 2000\(^{11}\)). Without information on case-control status, he used the complete pseudonymised study group 1 information gathered on external employments to develop a scheme to categorize external job phases on the background of his experiences and following the exposure assessment approach developed by Siemiatycki 1991\(^{12}\). Asbestos, quartz, chromium VI, nickel, PAHs, and others were considered as potential carcinogenic agents. For each external employment he identified the three most predominant agents and assigned to each agent the probability of a lung cancer risk (no risk, potential risk, likely risk, guaranteed risk) and the intensity of exposure (no exposure, low exposure, moderate exposure, high exposure). We derived indicator variables for each agent. Each variable informed on whether a subject was ever exposed to the specific agent during any employment outside the plant. We also tried to compute each subject's cumulative years of exposure to each agent. Since we found that most of the agents were strongly correlated we decided to focus on former occupational exposure to quartz which showed the strongest relationship with lung cancer mortality. Also, a detailed analysis on the effect of former exposures to specific agents was not in our scope and would have been rather difficult due to the limited power of our study. Thus, external exposure to quartz was applied as a surrogate to adjust for ‘external exposure to a known lung carcinogenic substance’ in this study. Variables that refer to this expert rating of external exposures were additionally labelled with ‘B.-A.’ in parentheses.
World War II (WWII) participation as a German soldier and prisoner of war history

Subjects might also have received adverse exposures during times of service in the German Wehrmacht during WWII. We therefore established contact with the Deutsche Dienststelle für die Benachrichtigung der nächsten Angehörigen von Gefallenen der ehemaligen deutschen Wehrmacht (WASt 2005\(^{13}\)). The WASt keeps detailed information for times of service of nearly all former members of the former German Wehrmacht. We sent a list of all subjects of study group 1 born before Jan 1\(^{st}\) 1935 to the WASt and asked for all available information of WWII participation as a German soldier (blinded to case-control status). The WASt returned to us all available information on the tour of duty for these individuals. On the basis of the WASt data we entered a variable into our database which provided the information coded to ‘1’ and ‘0’ whether or not a subject had participated in WWII as German soldier in the Wehrmacht or in any of its associated organisations.

Prisoner of war (POW) history

Another concern was that study subjects might have experienced times as prisoner of war (POW) during and after World War II (WWII) which could have co-determined health status at their start of work at the plant. The first step was to identify potential sources of information on this topic. We made contact with seven institutions located all over Germany inquiring whether they could provide the needed information. Only the DRK Suchdienst München (National German Red Cross Tracing Service) gave a positive response (DRK Suchdienst 2005\(^{14}\)). The archive contained information from search requests made by relatives looking for persons who had not returned home after the war had ended, and also searched requests of persons who returned from the war or prison camps and were looking for their families or other relatives. From 1947 onwards all returning former Wehrmacht soldiers were registered and also all search requests were systematically dealt with. Between 1950 and 1955 1,388,600 German Wehrmacht soldiers were documented as still being missing (Deutsches Rotes Kreuz 1995\(^{15}\)). We prepared a list of all subjects of study group 1 born before Jan 1\(^{st}\) 1935 and searched the DRK Suchdienst archive in Munich for information on imprisonment in Allied prison camps (blinded to case-control status). All documents found in the archive were copied and entered into a structured database. We created a dichotomous variable informing on
whether a subject had an individual POW history that comprised imprisonment in allied camps until 1947 or longer.

**Data management and statistical analyses**

We performed a description of the relevant variables. The analytical multivariable analyses of the matched nested case-control study were based on conditional logistic regression using the Stata clogit command (StataCorp 2005). The algebraic similarity of the partial likelihood based on the Cox model as applied by Morfeld et al. 2006 to the conditional-logistic likelihood for the logistic regression (Prentice and Breslow 1978) guaranteed continuity of analyses.

We started with fitting a conditional logistic regression model for lung cancer mortality depending on cumulative carbon black exposure while adjusting for age at hire. A nested case-control study based on incidence density sampling should approximate the relative rate estimates of the full cohort analysis (Rothman and Greenland 1998). Thus, we compared the odds ratios estimated from the case-control approach by conditional logistic regression with the hazard ratio estimates from the Cox regression analyses presented by Morfeld et al. 2006 to check whether both approaches were consistent.

**Results**

*Descriptive Findings*

**Job histories and duration of work in selected sections/sub-sections**

The members of study group 1 had on average 2.2 job phases (maximum = 6, minimum = 1). 27% of the controls and 24% of the cases had ever worked in the furnace black plant section. On the average, cases who ever had worked in this section had worked 6.9 yrs (sd=8.3 yrs) whereas the controls who ever had worked in the furnace black section spent 12.0 yrs (sd=8.3 yrs) in this plant sub-section. In the lamp black plant sub-section the mean duration of work among cases who ever worked in that section was 15.6 yrs.
(sd=10.6 yrs) and 20.2 yrs (sd=11.9 yrs) for controls. The proportion of cases who had ever worked in this section was 20%, among controls 12%. The corresponding numbers for the gas black plant section were 28 %, 11.7 yrs (sd=10.3 yrs) for the cases and 24 %, 13.4 yrs (sd=13.4 yrs) for the controls. Obviously, cases and controls included in this nested case-control study spent longer working times in these plant sections than cohort 1 members on the average (cp. Table 2 in Morfeld et al. 2006\textsuperscript{2}). Due to the matching procedure controls were no longer representative for the exposure duration distributions of the cohort.

**Exposure to carbon black**

Depending on the chosen exposure model (cp. Morfeld et al. 2006\textsuperscript{2}) the average cumulative carbon black exposure ranged from 41.0 u-yrs to 46.7 u-yrs among controls and from 23.9 u-yrs to 30.7 u-yrs among cases (Table 1). The mean values of the controls differed from the averages given for cohort 1 in Table 3 of Morfeld et al. 2006\textsuperscript{2} demonstrating that the matched controls were no longer representative for the cumulative carbon black exposure distribution of the cohort.

Instantaneous (at a particular time) and average carbon black exposure intensity as well as the duration of carbon black exposure are shown in Table 2, applying a 10 year lag. Mean dust intensities the controls were exposed to, were higher than for the cases when the exposure models A and B were used but not when applying exposure models C and D. The instantaneous exposure was greater among controls under all exposure models, and the same was observed for duration of exposure. Since carbon black exposure intensity was decreasing across calendar time, instantaneous carbon black exposure intensity - occurring ten years before incidence time - was smaller on average than the mean carbon black exposure intensity up to ten years before.
Table 2
Average instantaneous, average mean carbon black exposure and average duration of exposure for controls and cases depending on the chosen exposure model under application of 10 years lag. (study group 1: 50 cases, 100 controls; std. dev.=standard deviation, u=carbon black score unit)

<table>
<thead>
<tr>
<th>Exposure Model</th>
<th>Instantaneous Carbon Black Exposure / u</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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<td>0.851</td>
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<td>0.538</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
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<td>1.39</td>
<td>0.615</td>
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<td>0.893</td>
<td>1.38</td>
<td>0.629</td>
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<td>0.893</td>
<td>1.38</td>
<td>0.629</td>
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<table>
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<tr>
<th>Exposure Model</th>
<th>Mean Carbon Black Exposure / u</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
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<td></td>
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<td>2.00</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>2.24</td>
<td>1.12</td>
<td>2.38</td>
<td>1.49</td>
</tr>
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<td>2.62</td>
<td>1.65</td>
<td>2.62</td>
<td>1.74</td>
</tr>
<tr>
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<td></td>
<td>2.62</td>
<td>1.65</td>
<td>2.62</td>
<td>1.74</td>
</tr>
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</table>

<table>
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<th>Exposure Model</th>
<th>Duration of Exposure / yrs</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>independent</td>
<td>11.06</td>
<td>9.19</td>
<td>14.63</td>
<td>11.31</td>
</tr>
</tbody>
</table>

Information on tobacco consumption

Information on tobacco consumption was available for 100 subjects in study group 1. According to the smoking data gathered by Wellmann et al. 2006\(^1\) smoking information was documented for 89 subjects in study group 1. Due to the distribution of missing information on tobacco consumption 15 strata had to be dropped resulting in 35 cases and 57 controls (study group 2) remaining for analysis. All cases and 48 (84.2\%) of the controls in study group 2 were ever-smokers. The percentage of ever-smokers agrees with findings from cohort 2 (cp. Table 4b in Morfeld et al. 2006\(^2\)). For ever-smokers among the cases the average cumulative tobacco consumption was 42.0 pack-yrs (sd=19.4 pack-yrs), for
ever smokers among the controls the mean consumption was 34.0 pack-yrs (sd=17.1 pack-yrs). The minimum pack-years recorded for a case in the study group 2 was 10.96 pack-yrs. After separating the whole study group 2 into subjects with less or equal cumulative consumption than 10.96 pack-yrs we considered 79.0% of the controls and 97.1% of the cases as ever-smokers leaving one case and 12 controls (21.0% of the controls) in study group 2 who were considered to be never-smokers according to our new definition.

External occupational exposures

The screening of the personnel and medical files for information on jobs performed by members of study group 1 outside the carbon black plant returned information on such jobs for 130 subjects. These subjects had 346 job phases recorded on external employment. For 208 of the phases a starting date and for 203 phases an ending date was found.

328 out of the 346 phases could be coded according to ISIC-2 and included the ISIC Code ‘0’ 42 times which meant “no job”. For all 130 subjects, at least one phase could be coded according to ISIC-2. Constraining the considered job phases to those phases that took place prior to the subjects’ last job phase at the carbon black plant yielded 304 phases. Excluding phases which were identified as military service further reduced the number of phases to 207, now affecting no longer 130 but 128 individuals. 190 of the 207 phases could be coded according to ISIC-2 with the four most coded industry codes ‘5’ (construction) for 26 phases, ‘381’ (manufacture of fabricated metal products) for 26 phases, ‘352’ (manufacture of other chemical products) for 21 phases, and ‘382’ (manufacture of machinery except electric) for 19 phases. We observed that 91% of the controls and 94% of the cases were ever exposed to at least one of the eight considered agents (Table 3 gives a more detailed overview by agent).
Table 3  
Percentage of cases and controls who were at least once exposed to an carcinogenic agent (CAREX* estimates) during an employment outside the carbon black plant (studygroup 1: 50 cases, 100 controls).

<table>
<thead>
<tr>
<th>agent</th>
<th>cases</th>
<th>controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>silica*</td>
<td>90%</td>
<td>74%</td>
</tr>
<tr>
<td>cadmium</td>
<td>88%</td>
<td>74%</td>
</tr>
<tr>
<td>nickel</td>
<td>80%</td>
<td>69%</td>
</tr>
<tr>
<td>arsenic</td>
<td>92%</td>
<td>84%</td>
</tr>
<tr>
<td>chromium</td>
<td>80%</td>
<td>76%</td>
</tr>
<tr>
<td>diesel fumes</td>
<td>12%</td>
<td>23%</td>
</tr>
<tr>
<td>beryllium</td>
<td>80%</td>
<td>69%</td>
</tr>
<tr>
<td>asbestos</td>
<td>30%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Kauppinen et al. 2000  
# crystalline silica

Analytical findings

Comparison of results from Cox regression and conditional logistic regression analyses

The comparison of the conditional logistic regression analysis of lung cancer mortality for the complete study group (study group 1: 50 cases, 100 controls) and the findings by Morfeld et al. 2006 obtained by Cox regression analysis for cohort 1 was based on two models: the first model only included cumulative carbon black exposure (exposure model C), the second model additionally included age at hire as a covariate. The Cox regression models were additionally adjusted for date of birth to be comparable to the matched case-control analyses.

As expected, variances of the coefficients were smaller in the Cox analyses because all controls were used in this statistical approach but only two in the conditional logistic regression analysis. We observed a deviation of the odds ratio associated with cumulative carbon black exposure from the hazard ratio of 0.37 standard deviations of the hazard ratio (first model comparison) or 0.051 standard deviations (second model comparison). For the age at hire variable the difference was -0.27 standard deviations.
Analysis of tobacco consumption

We explored the association of smoking and lung cancer mortality in study group 2 by fitting a conditional logistic regression model with smoking status as independent variable. This model yielded an odds ratio of 9.27 (p=0.036) for subjects who were ever-smokers, i.e., subjects who had reported during an occupational medical examination to have actively smoked at some point in time and consumed tobacco of at least 10.96 pack-yrs. Additionally, we fitted the same model extended by entering the pack-years information. Here, the odds ratio for having ever smoked was 3.77 (p=0.269) and we found an odds ratio of 1.51 per 20 pack-yrs (p=0.132). For study group 4 the observed odds ratios were somewhat lower and not significant [data not presented].

Discussion

Extended summary of the work so far presented in the article

This study is the first nested case-control study on lung cancer mortality in an industrial cohort of carbon black workers. We conducted our study on 50 lung cancer cases and 100 calendar time- and age-matched controls (131 workers) selected from the cohort of German carbon black production workers as described in Wellmann et al. 2006 and Morfeld et al. 2006. Since we did not contact workers or next of kin to gather information by interview our study does not suffer from recall bias or related non-differential misclassification as emphasized as a particular problem of case-control studies (Breslow and Day 1980). For a detailed analysis we split the complete study group into three subgroups: subjects with information on tobacco consumption, subjects who hired after Jan 1st 1960 (restriction to inception cohort members), and subjects who belonged to the latter group and also having information on tobacco consumption available. We re-collected job histories and information on tobacco consumption from personnel and other paper files at the plant. Job histories were used to determine each subject’s exposure to carbon black. Further, following the suggestions made by Morfeld et al. 2006 we gathered information on WWII participation and individual POW history, external employments and on possible internal co-exposures to lung carcinogens. We would like to emphasize that the variables for WWII participation and individual POW history were established by us in order to adjust for possible selection biases, and as far as we know the use of such variables is unprecedented in occupational epidemiological studies. We described all data and performed statistical analyses using multivariable conditional logistic regression models for
lung cancer mortality depending on carbon black exposure. The models were fitted adjusting for various combinations of variables reflecting war-related exposures, external exposures, internal exposures, duration of work in selected plant sections/sub-sections, and tobacco consumption. The main result of the analyses was that we found no evidence for carbon black acting as a lung carcinogen for these carbon black exposed workers – thus repeating the general finding of no positive association between carbon black exposure and lung cancer mortality from cohort analyses while additionally adjusting for potential confounders in the nested case control study that could not be taken into account in the cohort investigation. In nearly all of our models the associated odds ratio for carbon black exposure was below one which may be suggestive of a protective characteristic of carbon black as it may have bound other gaseous carcinogens and thus reduced their bioavailability (cp. Morfeld et al. 2006\(^2\)). Morfeld et al. 2006\(^2\) also discussed - besides selection biases - the possibility that due to a threshold effect no positive exposure-response relationship may be observed in occupational epidemiological studies on carbon black workers.

**Discussion of the results from the comparison of structurally equivalent models**

The high similarity of the results for structurally equivalent models fitted in the cohort analysis and in the nested case-control approach is supportive of the successful incidence density sampling of the matched controls. Thus, this allows us to interpret odds ratios estimated in the analysis of the nested-case control study as being representative for the rate ratio of the cohort.

**Discussion on possible association of plant section with lung cancer mortality**

The analyses, which included indicators of work in selected sections/sub-sections, showed a positive association of lung cancer mortality with working in the lamp black sub-section, similar to a finding in the cohort analyses (Morfeld et al. 2006\(^2\)). This could be caused by exposures related to the lamp black production process or by other section-related circumstances. Subjects who worked in the lamp black section could also have been exposed to bulk shales which consisted of about 50% of crystalline silica (personal communication by plant management). Bulk shales were used in the ‘Kollerei’ sub-section of the preparation section, and it was reported to us by senior plant staff that in earlier times some of the subjects working in the lamp black section were also working in the
'Kollerei'. Another co-exposure which probably occurred was exposure to polycyclic aromatic hydrocarbons (PAH) and the variable “contact to feedstock oil” was positively associated with lung cancer mortality in our study. Tsai et al. 2001\textsuperscript{20} described the occurrence of PAH in the feedstock oil and the exposure to PAHs at the furnace oil pyrolysis carbon black production process, while Tsai et al. 2001\textsuperscript{21} expanded on the characteristics of exposure profiles for workers dealing with this type of carbon black production. Measurements taken at the lamp black section also indicated the historical presence of PAHs (personal communication by plant management). Thus, we would surmise that due to the way lamp black was produced historically, e.g., partial combustion of feedstock oil in pans which were opened time and again during a shift (semi-continuous process), workers might have received rather high PAH exposures. The production process and ventilation systems were optimized in the 1990s which reduced the PAH exposure of the workers in the lamp black section remarkably (personal communication by plant management). However, insufficient adjustment for smoking (see below), severe power limitations and presumably related sparse data upward biases (see below) and the fact, that no positive relationship between duration of work in the lamp black department could be established in this case-control approach (in contrast to the cohort analysis) definitely limit the findings about possible cancer risks in relation to the lamp black section. We consider our findings as only weak and inconclusive, indicative at most. A further follow-up of this study and parallel analyses of other carbon black worker studies may help to overcome these shortcomings.

**Discussion on Tobacco Consumption**

We entered the information on tobacco consumption time-dependently into our regression models. In comparison to Morfeld et al. 2006\textsuperscript{2} the estimated odds ratio was definitely higher (about 9) than the hazard ratio (about 5 to 6) observed for the smoking indicator in the Cox regression analysis. Still, our estimates need to be considered as being conservative since the way we constructed the smoking indicator lead to an intended misclassification of some ever-smokers to never-smokers. This approach was necessary since all cases in our study were ever-smokers (smoking odds ratio = infinity). Consequently, our analysis underestimated the effect of smoking on lung cancer mortality in our study group. For the analysis of potential biases of the lung cancer SMR observed
for the cohort, Morfeld et al. 2006\textsuperscript{22} tried to calculate the potential upward shift in the SMR caused by insufficient smoking adjustment.

We decided to assume that cigarette smoking started at an age of 21 years because this was the average age when subjects with information available started smoking in our study. To explore whether this decision was relevant, we recalculated the tobacco consumption assuming a starting age of 16 years for subjects with missing information. Recalculation of the model with its results presented in Table 8 yielded an increase in the odds ratio associated with “ever-smoker” from 12.0 to 14.3 (p<0.05), the odds ratio for cumulative exposure to carbon black did not change substantially. We further found that the odds ratio for smoking in the model presented in Table 10 increased from 10.70 (p=0.083) to 13.09 (p>0.054) when using the recalculated values, we also observed that the odds ratio for cumulative exposure to carbon black did not change relevantly. Therefore, we think that our approach proved to be a conservative one trying not to overestimate the influence of smoking.
References


