# Carbon Black and Lung Cancer Mortality —A Meta-regression Analysis Based on Three Occupational Cohort Studies

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# Carbon Black

- The effects of exposure to “poorly soluble particles with low acute toxicity (PSLTs )“ on human health are again the focus of research.
- In 2006, the International Agency for Research on Cancer (IARC) classified carbon black as “possibly carcinogenic to humans” (Group 2B) primarily on the basis of positive lung cancer findings in the rat.
- Evidence in human was **inconsistent**: increased lung cancer mortality was indicated in the UK and the German cohorts, while deficit was found in the US cohort.
- **Lack of exposure-response analyses** was identified to be a gap by the IARC working group (Ward 2010).
- An updated follow-up study of the US cohort was published in 2015, to address the exposure-response relationship (Dell et al, 2015).

# Exposure-response relationship

- ERR is an important criterion for assessing causal relationship in epidemiological research (Hill, 1965).
- Exposure-response relationship (ERR) is a useful concept to investigate an existing trend and can be expressed as a function of increasing exposure
- For risk assessment, exposure-response relationship can be performed to project:
  - exposure scenario has not yet occurred
  - a sufficient latency period since exposure has not yet passed

# Review of CB studies – external analysis

| Cohort | Study | Follow-up | Study population | Cause of deaths | # of deaths | SMR | 95% CI | Referent rates | Adjust |
|---|---|---|---|---|---|---|---|---|---|
| **US cohort** | Dell et al. 2006 | 1930 - 2003 | Full cohort 5011 | All causes | 1326 | 0.74 | 0.70 – 0.78 | State | no |
| | | | 18 CB facilities | All malignant | 330 | 0.83 | 0.74 – 0.92 | | |
| | | | | Lung cancer | 138 | 0.97 | 0.82 – 1.03 | | |
| | | | | NMRD | 120 | 0.99 | 0.83 – 1.18 | | |
| | Dell et al. 2015 | 1940-2011 | Full cohort 6634 | All causes | 1947 | 0.78 | 0.75 – 0.82 | State | no |
| | | | incl. inception cohort 4882 | All malignant | 512 | 0.79 | 0.72 – 0.86 | | |
| | | | | Lung cancer | 184 | 0.77 | 0.67 – 0.89 | | |
| | | | | NMRD | 163 | 0.88 | 0.75 – 1.02 | | |

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| Cohort | Study | Follow-up | Study population | Cause of deaths | # of deaths | SMR | 95% CI | Referent rates | Adjust |
|---|---|---|---|---|---|---|---|---|---|
| **UK cohort** | Sorahan et al. 2001 | 1951 - 1996 | 1,147 male | | | | | England and Wales | no |
| | | | 5 facilities | All cause | 372 | 113 | 1.02 – 1.25 | | |
| | | | | All malignant | 137 | 1.42 | 1.19 – 1.68 | | |
| | | | | Lung cancer | 61 | 1.61 | 1.29 – 2.00 | | |
| | | | | NMRD | 35 | 1.07 | 0.75 – 1.49 | | |

# Review of CB studies – external analysis

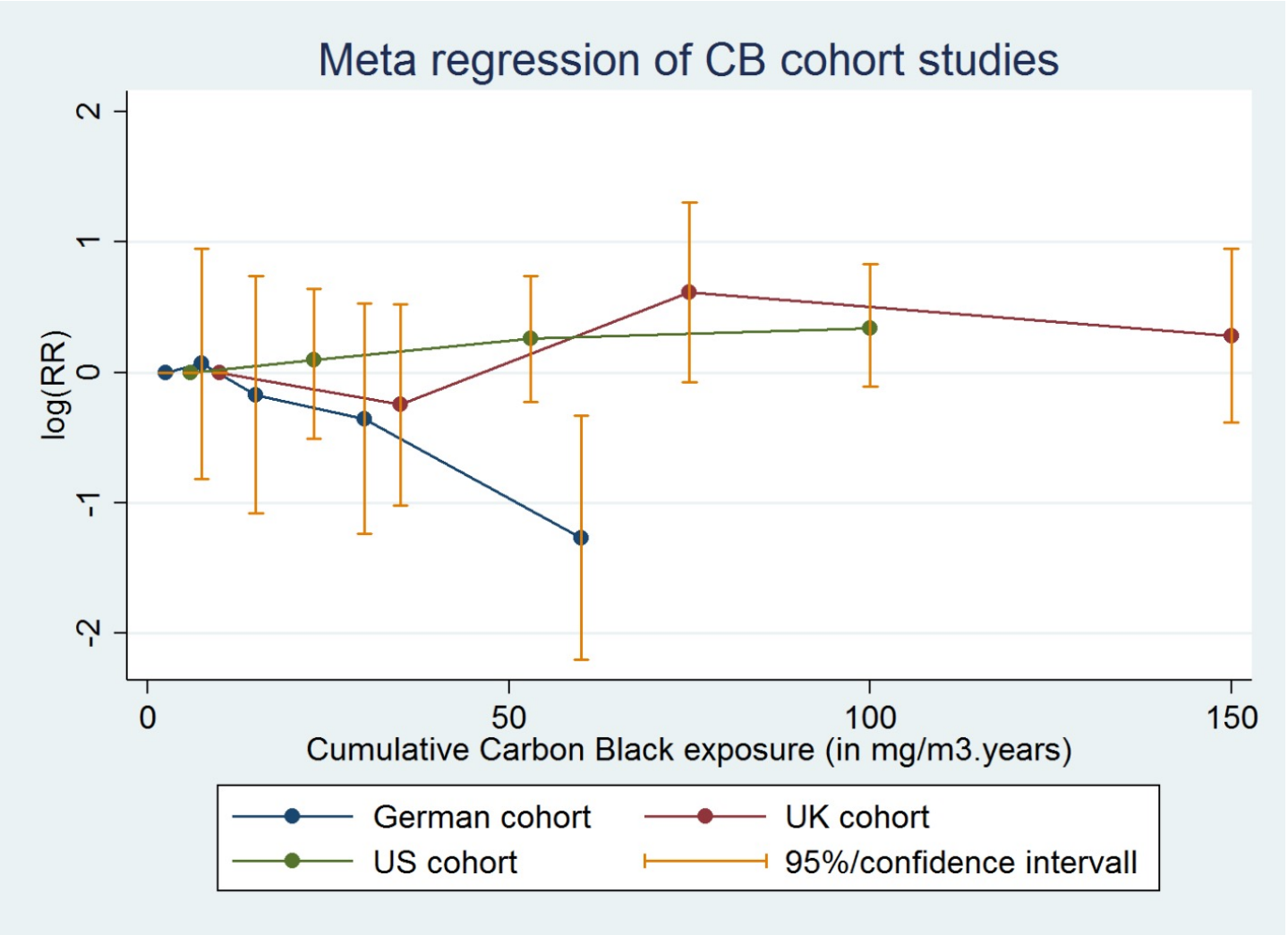
| Cohort | Study | Follow-up | Study population | Cause of deaths | # of deaths | SMR | 95% CI | Referent rates | Adjustment |
|---|---|---|---|---|---|---|---|---|---|
| **German cohort** | **Wellmann et al. 2006** | 1976 - 1998 | 1,522 blue collar workers | | | | | (west) German population | no |
| | | | | All cause | 332 | 1.20 | 1.08 – 1.34 | | |
| | | | | Lung cancer | 50 | 2.18 | 1.61 – 2.87 | | |
| | | | | NMRD | 18 | 1.14 | 0.68 – 1.80 | | |
| | **Morfeld et al. 2006a** | | Full cohort 1,528 | All cause | 328 | 1.23 | 1.10 -1.37 | West Germany | |
| | | | Incl. Inception cohort 1,271 | | 328 | 1.17 | 1.05- 1.30 | North-Rhine Westphalia | |
| | | | | | 328 | 1.20 | 1.07 – 1.34 | Cologne | |
| | | | | Lung cancer | 47 | 1.33 | 0.98 – 1.77 | West Germany | Smoking, prior exposure |
| | | | | | 47 | 1.27 | 0.93 – 1.69 | North-Rhine Westphalia | Smoking, prior exposure |
| | | | | | 47 | 1.20 | 0.88 – 1.59 | Cologne | Smoking, prior exposure |

# Overview of external analyses of CB studies

| | Study | Cause-specific SMR (95% CI) | | | |
|---|---|---|---|---|---|
| | | **All cause** | **All malignnant** | **Lung cancer** | **NMRD** |
| US cohort | Dell et al. 2006 | 0.74 (0.70 – 0.78) | 0.83 (0.74 – 0.92) | 0.97 (0.82 – 1.03) | 0.99 (0.83 – 1.18) |
| | Dell et al. 2015* | 0.78 (0.75 – 0.82) | 0.79 (0.72 – 0.86) | 0.77 (0.67 – 0.89) | 0.88 (0.75 – 1.02) |
| UK cohort | Sorahan et al. 2001 | 1.13 (1.02 – 1.25) | 1.42 (1.19 – 1.68) | 1.61 (1.29 – 2.00) | 1.07 (0.75 – 1.49) |
| German cohort | Wellmann et al. 2006 | 1.20 (1.08 – 1.34) | | 2.18 (1.61 – 2.87) | 1.14 (0.68 – 1.80) |
| | Morfeld et al. 2006a** | 1.20 (1.07 – 1.34)# | | 1.20 (0.88 – 1.59)# | |

* Updated analyses of Dell et al. (2006)
** Re-analyses of Wellmann et al. 2006
# regional referent population, with adjustment for smoking and prior exposure

# Exposure in relationship with lung Ca. mortality



# Meta regression

- Combine the data of 13 categories of cumulative exposure and the category-specific risk estimates
- Two-stages hierarchy modelling
  - To estimate the exposure–response association within a particular study
  - A log linear model for random-effects exposure–response meta-regression:

$$\ln RR = \beta(\text{exposure}) + \varepsilon, \text{ where}$$
$$\beta = \text{the common slope associated with CB exposure across studies,}$$
$$\varepsilon = \text{the random effect between the studies.}$$

- RR provides a risk estimate per unit increase of cumulative exposure
- Repeated sensitivity analyses

# Exposure-response relatiponship wrt. lung Ca.

| Study | Lag = 0 yr | | | Adjustment |
|---|---|---|---|---|
| | Estimate (SE) | *P* | RR (95%CI) | |
| **Dell et al. 2015 only** | 0.0028 (0.0019) | 0.1395 | 1.0052 (0.999 – 1.006) | Attained age, decade of birth, age at hire, plant |
| **Sorahan et al. 2001 only** | 0.0100 (0.0052) | 0.0567 | 1.010 (0.997 - 1.020) | Attained age, duration of employment, employment status, year of hire, plant |
| **Wellmann et al. 2006 only** | -0.0199 (0.0069) | 0.0040 | 0.980 (0.967 - 0.994) | Attained age, smoking |
| **All studies combined** | **-0.0013 (0.0065)** | **0.8469** | **0.999 (0.986 – 1.012)** | |

# Sensitivity analysis
# - cumulative exposure-response estimates

| Study | Estimate (SE) | P | RR (95%CI) | Adjustment |
|---|---|---|---|---|
| | **Lag = 0 yr** | | | |
| **Dell et al. 2015 only** | 0.0028 (0.0019) | 0.1395 | 1.0052 (0.999 – 1.006) | Attained age, decade of birth, age at hire, plant |
| **Sorahan et al. 2001 only** | 0.0100 (0.0052) | 0.0567 | 1.010 (0.997 - 1.020) | Attained age, duration of employment, employment status, year of hire, plant |
| **Morfeld et al. 2006b only** | -0.0094 (0.0085) | 0.2675 | 0.9906 (0.974 - 1.007) | Attained age, date of birth, age at hire, prior exposure |
| **All studies combined** | **0.0030 (0.0038)** | **0.4252** | **1.003 (0.996 – 1.010)** | |

# Sensitivity analysis
# - cumulative exposure-response estimates

| Study | Estimate (SE) | P | RR (95%CI) | Adjustment |
|---|---|---|---|---|
| | **Lag = 20 yrs** | | | |
| **Dell et al. 2015 only** | 0.0029 (0.0018) | 0.1003 | 1.0029 (0.9994 – 1.0064) | Attained age, decade of birth, age at hire, plant |
| **Sorahan et al. 2001 only** | -0.0026 (0.0027) | 0.3269 | 0.9974 (0.9921 - 1.0026) | Attained age, duration of employment, employment status, year of hire, plant |
| **Morfeld et al. 2006b* only** | -0.0099 (0.0106) | 0.3502 | 0.9901 (0.9698 – 1.0109) | Attained age, date of birth, age at hire, prior exposure |
| **All studies combined** | **-0.0001 (0.0026)** | **0.9754** | **0.9999 (0.9947 – 1.0051)** | |

# Discussion

- Contradicting results from the external and the internal analyses from Wellmann et al. (2006).
- Lack of adjustment for smoking lead substantial to an over-estimation of SMR for lung cancer in German cohort (Morfeld et al. 2006a).
- Heterogeneity between the studies hampers summarizing SMRs.
- Other possible reasons for heterogeneity:
  - missclassification
  - exposure assessment
- Combining the results from internal analyses across the studies, no / slightly decreasing exposure-response relationship can be concluded.

# Discussion

- **Biological plausibility**
  - Evidence in human might be attributed to toxicokinetic difference of handling inhaled dusts; interstitialization accumulation in humans versus alveolar accumulation in rats
- **Consistency**
  - Negative dose-response relationship was found in studies of TiO2 and lung cancer risks
- **Dose-response relationship**
  - Overall, slightly negative exposure – response relationship was found
  - Causal relationship between exposure to CB and lung cancer can not be concluded