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Epidemiological evaluation of exposure-response relationships for crystalline silica and risk of silicosis and lung cancer: Implications for regulation and prevention

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Confirmed health effects of silica

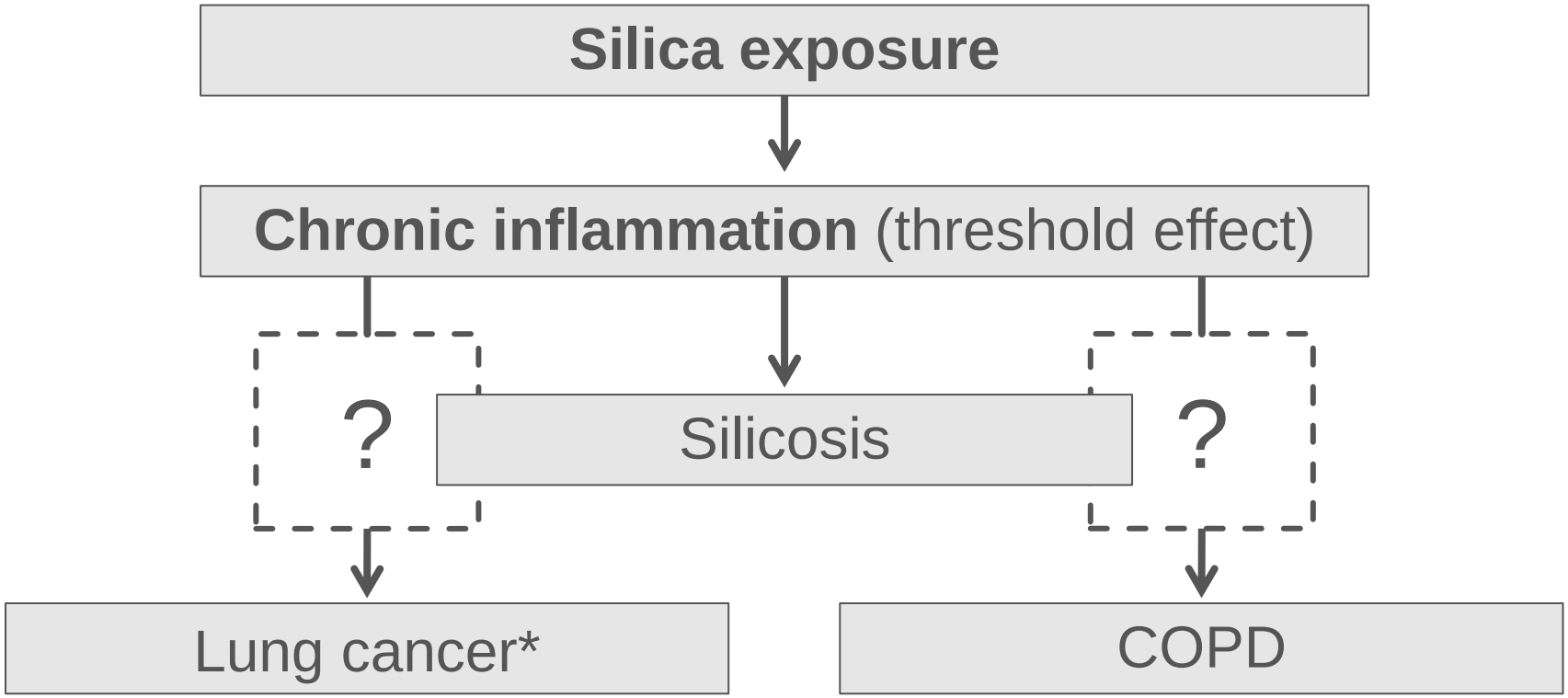
Pulmonary inflammatory reaction

- Silicosis
- Cancer
- Chronic obstructive pulmonary disease (COPD)

Non-linear exposure-response relationship / threshold?

Health-based threshold limit value (TLV)?

Proposed mechanism



* Genotoxicity of minor relevance

Epidemiological data

Chronic inflammation: no data

- Silicosis: Many studies mostly grade 1/1 – manifestation of weak chronic pulmonary inflammation; few with quantitative exposure data
  Major problems: Uncertainty of radiological diagnosis, long-term exposure assessment
- Lung cancer: Many studies
  Major problems: Quantification of cumulative exposure, smoking as confounder
- COPD: Many studies, few with quantitative exposure information

COPD

Longitudinal studies, good long-term exposure data for respirable crystalline silica (RCS), smoking and other confounders required

Recent critical review of epidemiological data
(Hoet et al. Crit Rev Toxicol 2017):

"Supporting evidence in favor of a qualitative association" between RCS exposure and obstructive lung dysfunction

"No convincing evidence of an exposure-response relationship" between RCS exposure and obstructive lung dysfunction

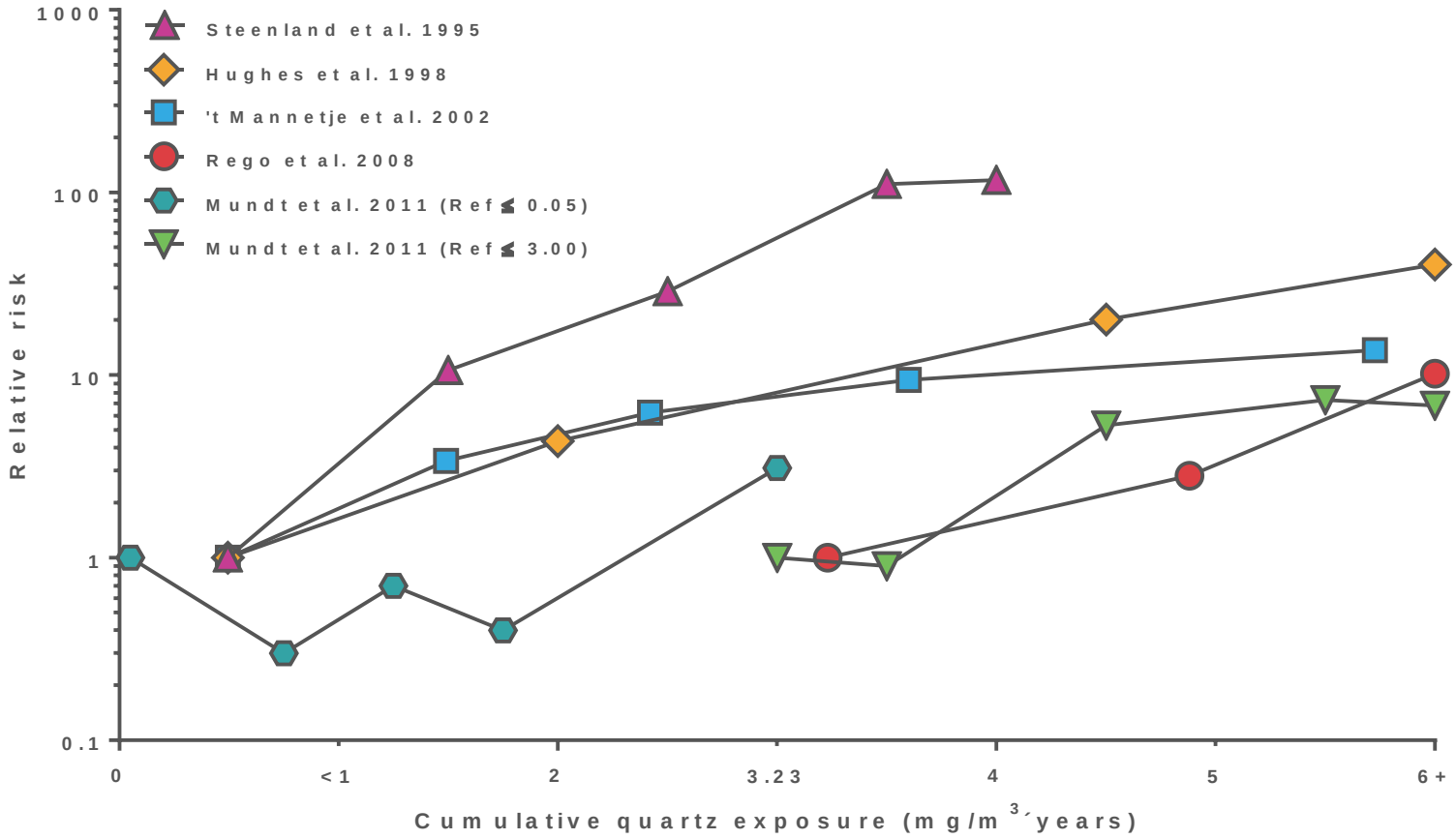
"Considerable uncertainties" because of limitations in exposure or lung function assessment

"No well-founded quantitative estimates can be drawn."

Exposure-response relationship / TLV

- Quantitative assessment based on inflammation / COPD not possible / reliable
- Focus on epidemiological data for silicosis 1/1 and lung cancer
- Mechanism comparable to granular biopersistent dust (with additional specific toxicity): Chronic inflammation with threshold
- Threshold vs. non-threshold (linear) models?

Silicosis – true differences between studies?



Silicosis – *Steenland et al. and ‘t Mannetje et al.*

Steenland et al.:

- 3330 Gold miners working underground between 1940 and 1965
- Diagnosis based primarily on death certificates
- RCS content estimated based on 82 respirable dust samples from 1970s

‘t Mannetje et al.:

- Includes data from six cohorts ***(also Steenland et al.)***
- Median average and cumulative exposures differ up to factor of 50 between cohorts

Silicosis – *Hughes et al.*

- 1809 workers in the diatomaceous earth industry with employment period between 1942 and 1987
- Quantitative air-monitoring data available since 1948
- Regular but not mandatory chest x-rays
- 81 Workers diagnosed with silicosis >=1/0 in their last reading
- If average RCS exposure > 500 µg/m^3: significantly increased silicosis risk for cumulative exposures > 1 mg/m^3-years
- For lower average exposures risk of silicosis with around 1% comparable to unexposed populations

Silicosis – *Rego et al.*

- Cross-sectional study (chest x-rays) in 440 granite workers between 2004 and 2005
- Quantification of RCS exposure from 1991 onwards with retrospective extrapolation
- 73 of 77 cases of silicosis (1/1) with cumulative exposures > 3.5 mg/m^3-years
- Not significantly increased silicosis risk in workers in the third quintile of RCS exposure (around 5 mg/m^3-years)

Silicosis - *Mundt et al. and Morfeld et al.*

German Porcelain Industry *(Mundt et al.)*

- 17,144 Workers
- Inclusion criterium: Participation in a medical screening program for silicosis between 1985 and 1987
- Observation for mortality and silicosis (1/1) morbidity through 2005
- Calculation of individual annual RCS concentrations based on > 8,000 historical measurements

Evaluation of a TLV *(Morfeld et al.)*

- Cox regression with age as time variable adjusted for gender and smoking status
- Comparison of threshold – non-threshold models

Silicosis - *Mundt et al. and Morfeld et al.*

Porcelain industry results

- Best threshold estimate: 250 µg/m³ (95% CI: 160-300 µg/m³)
- Some silicosis cases even after exposures between only 0-150 µg/m³ – „background rate“ / misclassification?
- High short-term exposures potentially of higher relevance
- Altogether silicosis risk increased at RCS concentrations > 150 µg/m³

Silicosis in Sweden

Reported cases of silicosis in Sweden in 1926-2001

Period	Annual number of new cases*
1926-1930	2
1931-1935	56
1936-1940	87
1941-1945	110
1946-1950	107
1951-1955	75
1956-1960	41
1961-1965	54
1966-1970	63
1971-1975	45
1976-1980	33
1981-1985	25
1986-1990	8
1991-1995	4
1996-2001	2

* The mean annual numbers in each 5-year period is presented

TLV: 100 µg/m^3 since 1978

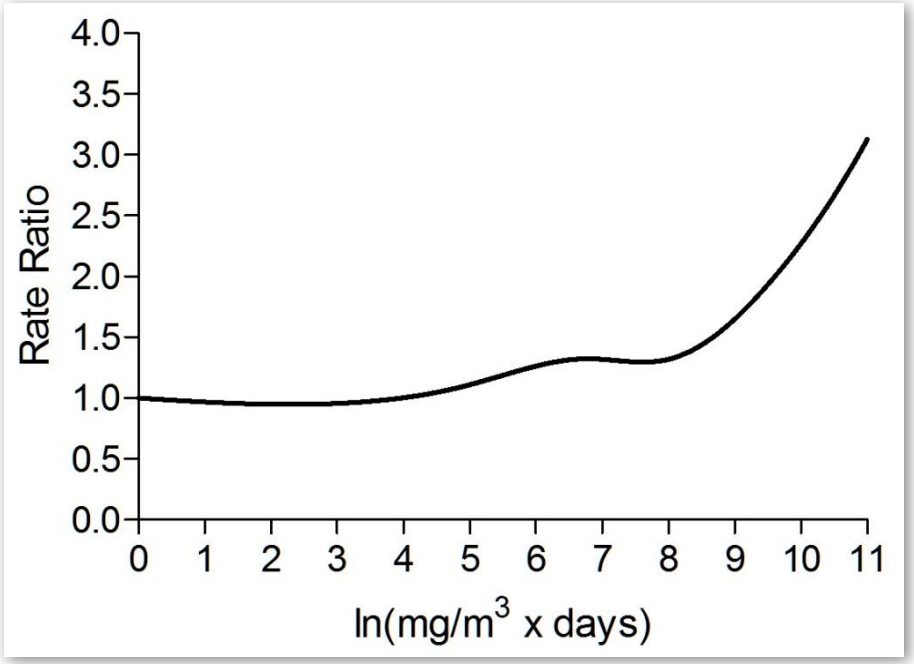
Torén and Sterner. Scand J Work Environ Health. 2003;29:239-245

Lung cancer - *Steenland et al.*

- Pooled analysis of 10 studies (N=65,980)
- Pronounced differences in average and cumulative exposures
- Lack of detailed and historical exposure data
- Majority of studies without smoking data
- Considerable heterogeneity of results by study, especially for average and cumulative exposure
- Valuable in demonstrating a clear cancer risk with higher exposures

Steenland et al. Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica exposed workers: an IARC multicentre study. Cancer Cases and Control. 2001;12:773-784

Lung cancer– Exposure-response



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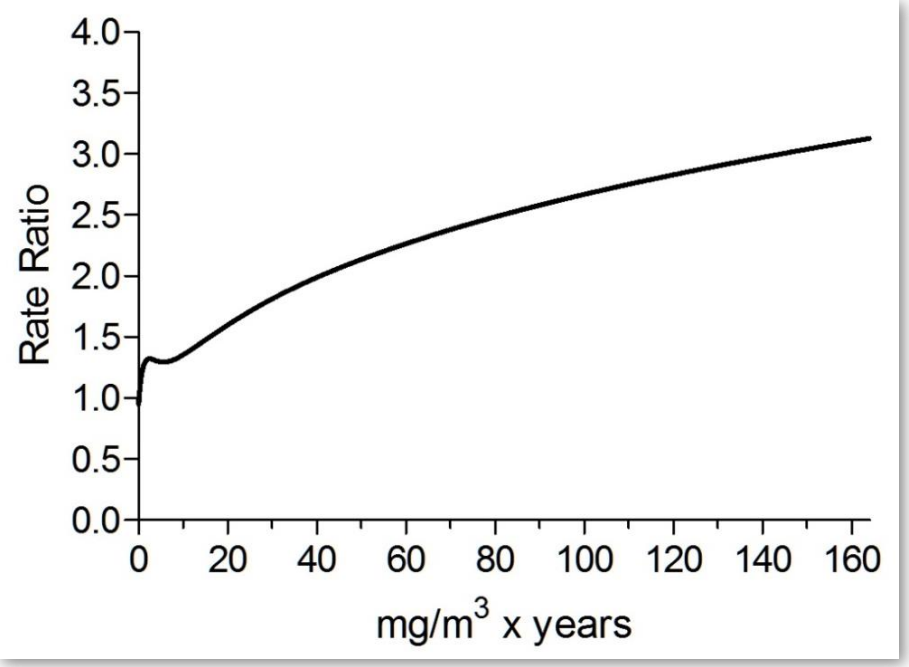
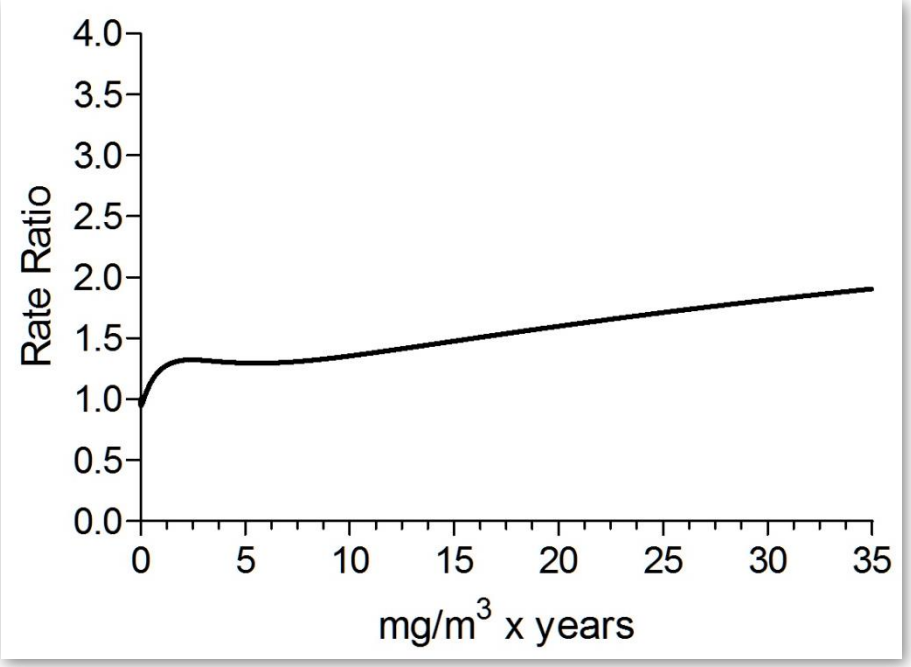
Lung cancer – Rescaling of exposure-response





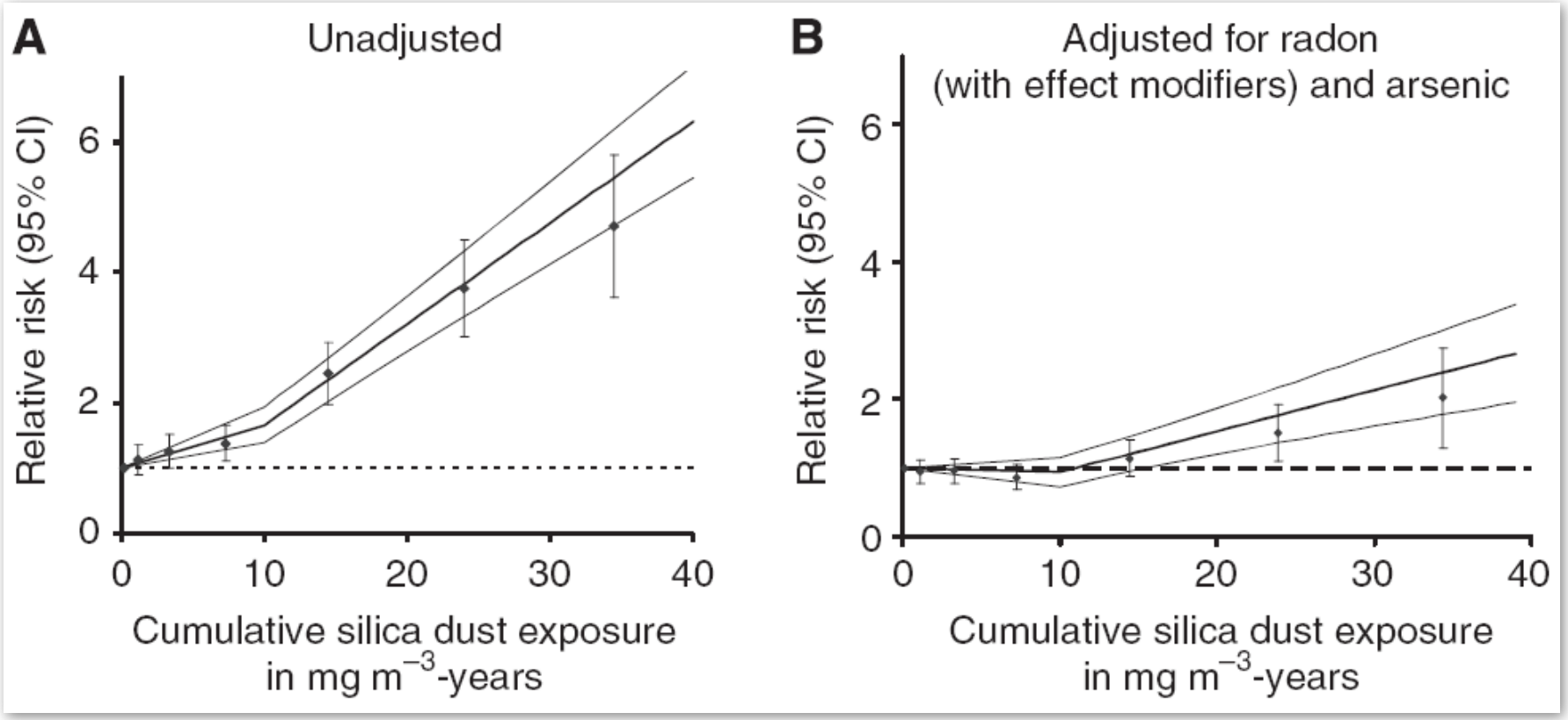
Steenland et al. Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica exposed workers: an IARC multicentre study. Cancer Cases and Control. 2001;12:773-784

Lung cancer – *Sogl et al.*

- German uranium miners (Wismut cohort; nearly 60,000 workers)
- Employment at least 6 months between 1946 and 1989
- By 2003 almost 3,000 lung cancer deaths
- Systematic RCS and fine dust measurements available from 1960
- Development of a detailed job-exposure matrix also for previous years including radon and arsenic exposures
- Limitation: smoking data only available for participants of a nested case-control study (no trend with increasing silica exposure)

Sogl et al. Quantitative relationship between silica exposure and lung cancer mortality in German uranium miners, 1946-2003. British Journal of Cancer. 2012;107:1188-94

Lung cancer – *Sogl et al.*



Sogl et al. Quantitative relationship between silica exposure and lung cancer mortality in German uranium miners, 1946-2003. British Journal of Cancer. 2012;107:1188-94

Lung cancer – *Sogl et al.*

- Depending on selection of statistical model no increased lung cancer risk for average exposures up to 250 or 500 µg/m^3
- Relative RCS-dependent risks above 2 for high exposures
- Discussion about over-adjustment in the statistically best model including effect modifiers;
  but adjustment for radon (and arsenic) necessary
- Due to the high number of participants and good exposure assessment distinction between radon and silica effects possible

Sogl et al. Quantitative relationship between silica exposure and lung cancer mortality in German uranium miners, 1946-2003. British Journal of Cancer. 2012;107:1188-94

Lung cancer mortality in China

Cancer	Lifetime highest silica exposure					
	≤ 0.05 mg/m³		≤ 0.10 mg/m³		≤ 0.35 mg/m³	
	HR*	95% CI	HR	95% CI	HR	95% CI
1	1.47	0.88-2.47	1.53	1.07-2.20	1.43	1.10-1.86
2	1.36	0.77-2.39	1.30	0.89-1.90	1.29	1.00-1.68
3	1.58	1.00-2.50	1.64	1.16-2.30	1.75	1.37-2.24
4	1.29	0.76-2.19	1.20	0.83-1.74	1.76	1.32-2.36

* HR = Hazard ratio

Liu et al. Total and Cause-Specific Mortality Risk Associated With Low-Level Exposure to Crystalline Silica: A 44-Year Cohort Study From China. Am J Epidemiol. 2017;186:481–490

Risks after hypothetical intervention

- 2342 California diatomaceous earth workers regularly exposed to crystalline silica, followed between 1942 and 2011
- Comparison of an intervention setting a theoretical maximum exposure limit at 0.05 mg/m^3 / zero to observed exposure
- Risk ratios for lung cancer mortality:
  0.86 (95% CI: 0.63, 1.22) and 0.82 (95% CI: 0.53, 1.26)
- Risk ratios for non-malignant respiratory disease mortality:
  0.69 (95% CI: 0.52, 0.93) and 0.63 (95% CI: 0.43, 0.91)

Neophytou et al. Estimating Counterfactual Risk Under Hypothetical Interventions in the Presence of Competing Events: Crystalline Silica Exposure and Mortality From 2 Causes of Death. Am J Epidemiol. 2018;187:1942-1950

Conclusions

- Health-based TLV protective against silica-induced health effects
- No human evidence below which concentration first inflammatory effects can be excluded
- No evidence for silica-induced health effects
  if a TLV of 100 µg/m³ is implemented and its observation is strictly enforced over long term
- Need for a lower TLV because of scientific uncertainty?
- In Germany adoption of an evaluation standard of 50 µg/m³ instead of a TLV