Risk assessment in Germany: a critical view on the epidemiology, and rationale of the resulting recommended OEL

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Committee on Hazardous Substances (AGS)

- The AGS is a consultative body of the Federal Ministry of Labour and Social Affairs in Germany on issues of the Ordinance on Hazardous Substances
- Legal basis in section 20 of the Hazardous Substances Ordinance (GefStoffV)
- The AGS has about 25 members from all areas of occupational health and safety
- **Tasks:**
  (1) To determine how the requirements set out in the GefStoffV can be met and to develop the rules and findings corresponding to the respective state of technology and medicine, and
  (2) To advise the Federal Ministry of Labour and Social Affairs (BMAS) on all questions concerning hazardous substances.
- **Three subcommittees:**
  UA I “Management of hazardous substances” ["Gefahrstoffmanagement“]
  UA II “Safety measures” ["Schutzmaßnahmen“]
  UA III “Risk assessment for hazardous substances” ["Gefahrstoffbewertung“]

https://www.baua.de/EN/Tasks/Committee-administration/AGS/AGS_node.html

AGS on Diesel Engine Emissions (DEE)

- **Decision in May 2017: OEL = 50 µg REC/m³**
  (based on traditional diesel engine exhaust emissions)

- **Question: Exposure-response relationship or OEL ??**
  Decision criterion: What is the predominant mode of action,
  - genotoxicity ?
  - or particles effect?

Toxicological deduction (I)

- DEE are not a chemically clearly defined substance, but a mixture of substances
- The proportion of DEE that can be deposited on filters is known as diesel soot particle
- Diesel soot particles consist of insoluble cores of elemental carbon and other substances adsorbed on them, which are more or less soluble such as PAH (e.g. benzo[a]pyrene)

Toxicological deduction (II)

- What is the predominant mode of action?
- Carcinogenic effect primarily by ultra-fine particles
- Proportion of PAH in DEE was estimated quantitatively using BaP as the lead substance
- Acceptable risk (4:100,000) for BaP is 7 ng/m³
- Assuming that DPM contains 50% REC:
  - ⇨ 100 µg DPM / 50 µg REC(/m³) contain 0.23 ng(/m³) BaP (Heinrich et al., 1995; Liang et al., 2005)

Toxicological deduction (III)

- **Basic toxicological study:**
  Mauderly et al (1987) & Henderson et al (1988)

- **NOAEC (in rats): 350 µg/m³**

- **Conversion to humans by**
  a.) Human equivalent concentration model (HEC)
  b.) Multiple Path Particle Dosimetry Model (MPPD version 2.11)

- **Results: 72 µg REC/m³ (HEC); 34 µg REC/m³ (MPPD)**

- ⇨ **Final OEL: 50 µg REC/m³**

- **Details on www.baua.de (search for: AGS diesel)**
  82 pages (paper in german)

The decisive question

Do the results of the epidemiological studies require a further lowering of the limit value?

DIRECTIVE (EU) 2019/130 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 January 2019
50 µg/m³ REC (valid from 21 February 2023)

Health-based recommended occupational exposure limit of the Dutch Expert Committee on Occupational Safety (DECOS) – a permanent committee of the Health Council of the Netherlands (13 March 2019)
1.03 µg/m³ REC (as prohibition risk level)

IARC on DEE

- IARC classified DEE in June 2012 as "carcinogenic to humans"

- Key studies:
  1.) The Diesel Exhaust in Miners Study (DEMS)
  Attfield et al (2012) & Silverman et al (2012)
  2.) Cohort study on truck drivers
  Garshick et al (2012)

DEMS

The Diesel Exhaust in Miners Study (DEMS) is the most suitable data material to date to examine a possible link between DEE and lung cancer risk:

- Cohort of miners (from 8 non-metal mines),
  N > **12,000**; mean follow-up: **22,5 years** (until 1997)
- Dieselization between 1947 and 1967
- Sufficiently homogeneous (social status, lifestyle)
- Strong contrast in REC concentration, on average
  underground jobs: **128.2 µg/m³**
  surface jobs: **1.7 µg/m³**

Results of the a-priori-defined cohort analysis

2185 deaths:	SMR = 0.93 (95%CI: 0.89 - 0.97)
203 lung cancer deaths:	SMR = 1.26 (95%CI: 1.09 - 1.44)
including:	
Surface-only (N = 81)	SMR = **1.33** (95%CI: 1.06 – 1.66)
Ever-underground (N=122)	SMR = **1.21** (95%CI: 1.01 – 1.45)

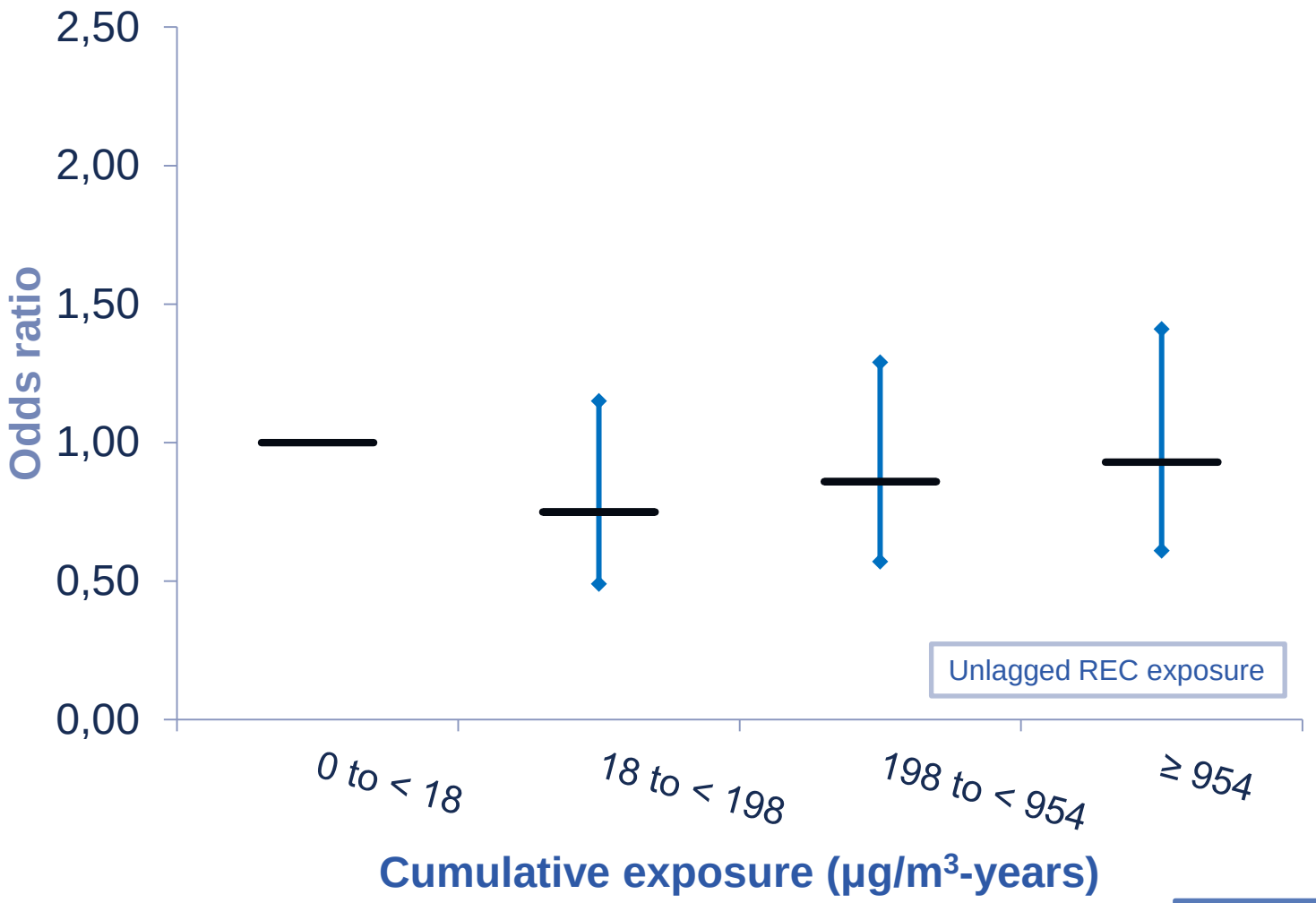
[Source: Attfield et al., 2012]

Internal analysis of the cohort

Cox Proportional Hazard Models:

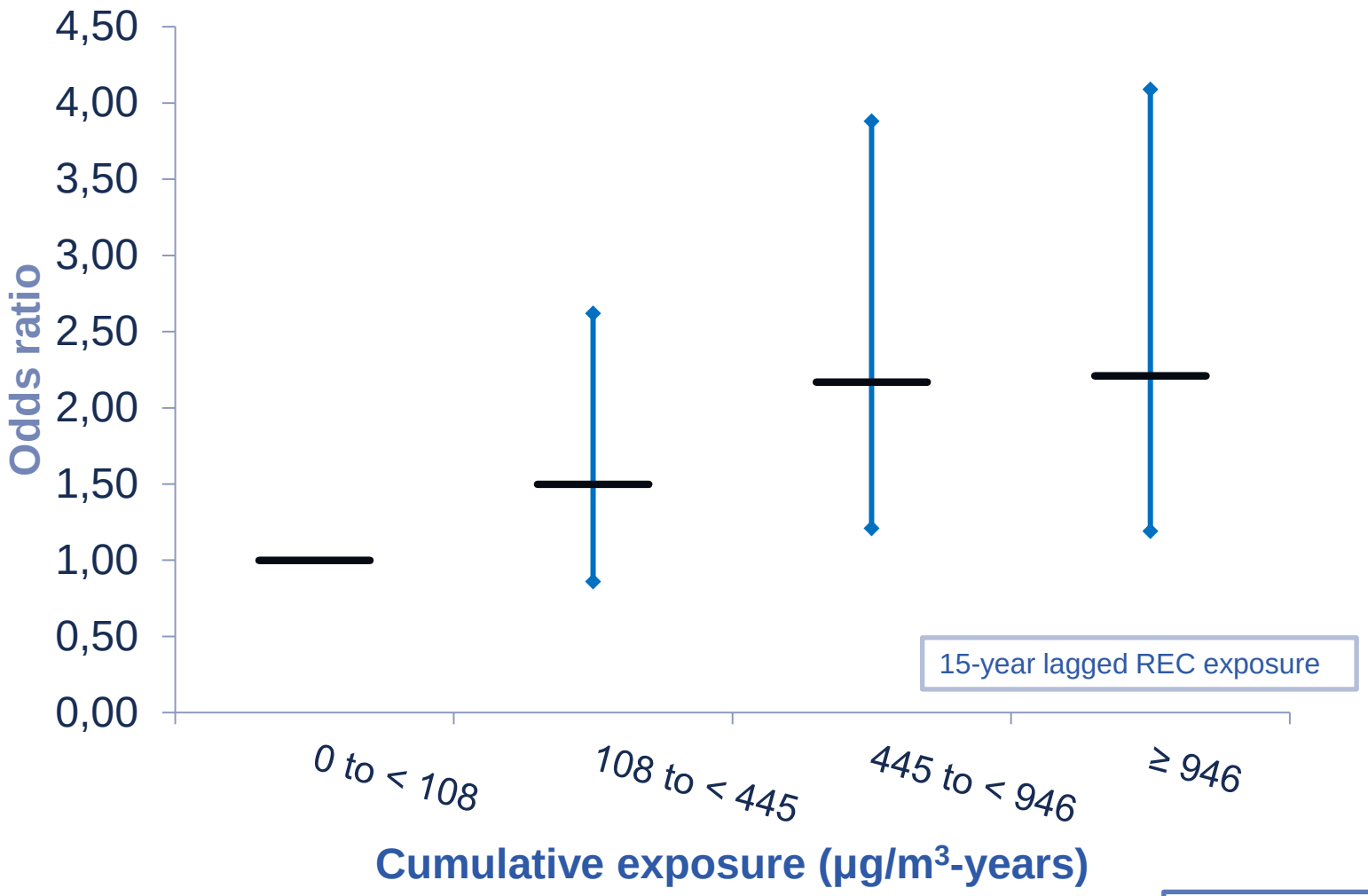
- $h(t) = \exp[\sum_1^k \beta_i x_i + \beta_{REC} x_{REC}] \times h_0(t)$
- t: attained age
- x_i: race/ethnicity, sex, and birth year
- x_{REC}: exposure metrics (REC intensity, cumulative REC without lagging or 15-year lagging
- Stratified by state (study facility location)

Complete DEMS-cohort (Attfield et al. 2012)



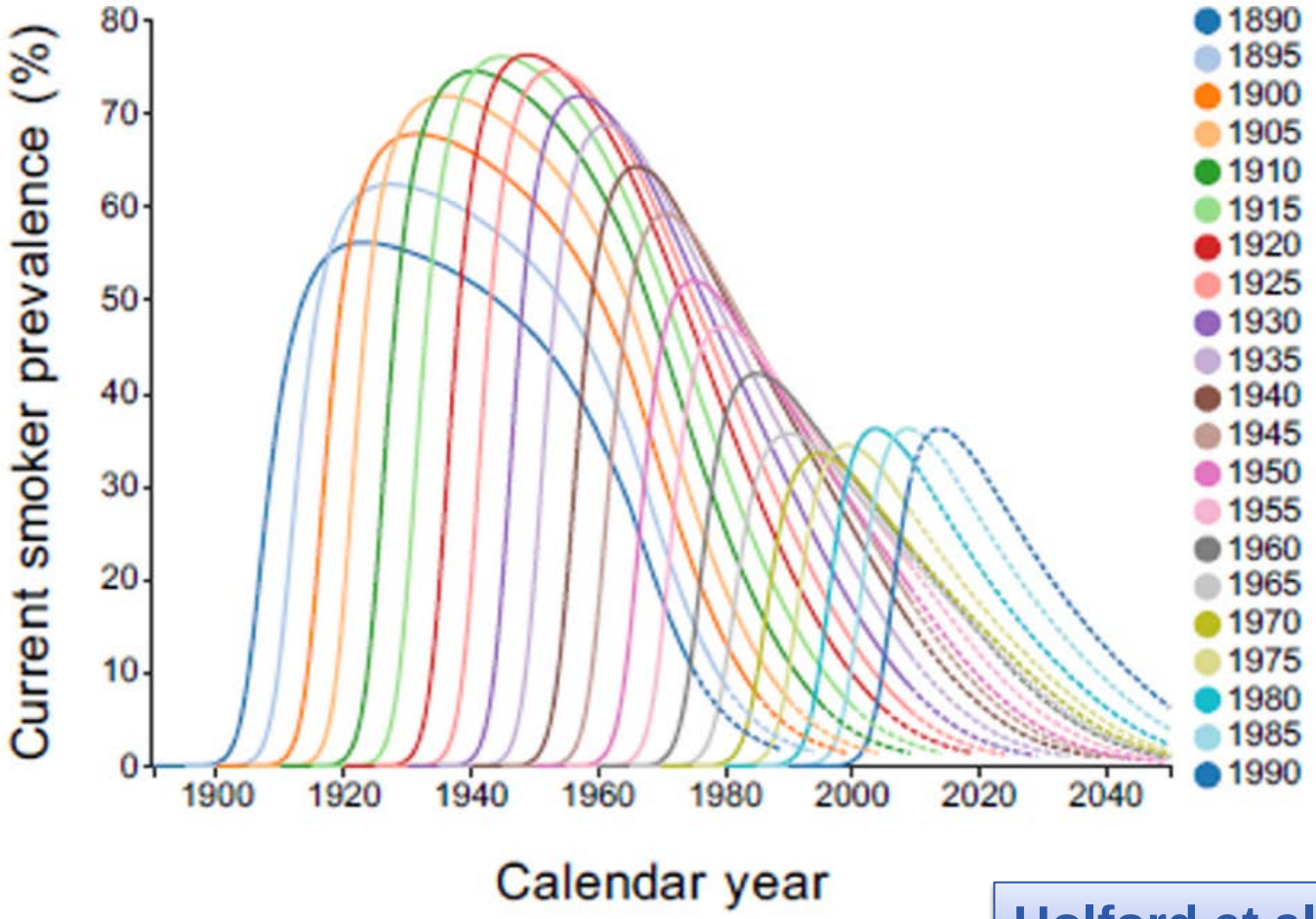
Source: Table S3

Ever-underground workers (Attfield et al. 2012)



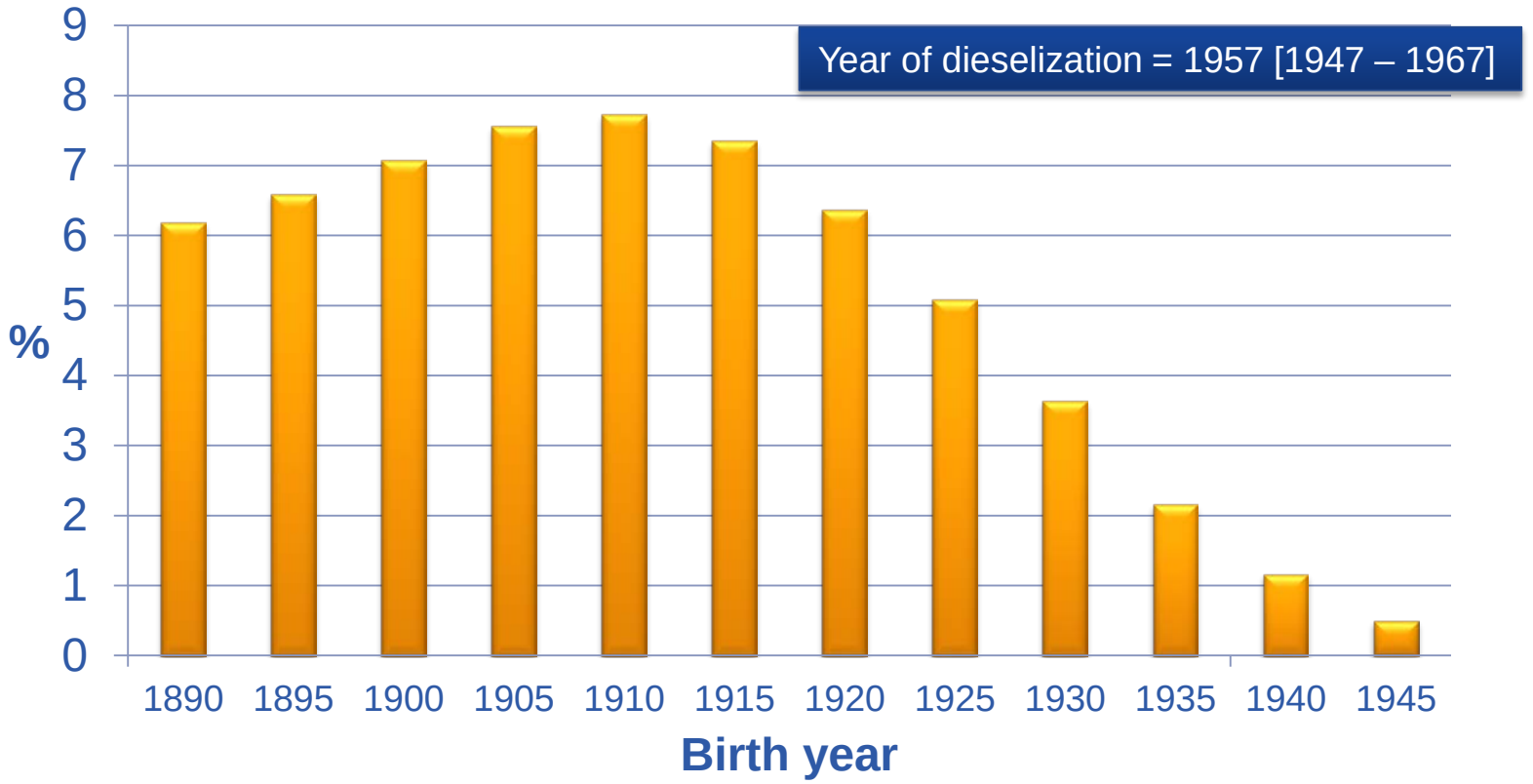
Source: Table 4

Current smoker prevalence, Males, U.S.



Holford et al., 2014

Cumulative Lung Cancer Mortality until 1997, U.S. (males) by birth year



Weaknesses of the cohort study

- ☹ The description of the cohort is insufficient [Information about the distribution of the year of birth, hire, first exposure, death etc. is missing]
- ☹ Inclusion of the birth year as a linear term seems not to be adequate
- ☹ The change underground ↔ surface workplace may have operational reasons but also medical. Hence, a useful (and possibly even better) categorization could be:
  work location at study entry

HEI Diesel Epidemiology Panel - SMR analysis

"Some reviewers of the DEMS study have argued that the higher SMRs for lung cancer in the surface-only workers, where REC exposures are lower, are inconsistent with an exposure–response effect (Hesterberg et al. 2012b). However, these results should not be overinterpreted for the following reasons. First, these analyses cannot take into account any covariates (e.g., smoking, other occupational exposures) that could differ between the study cohort and the general population. " (p. 55)

Case-control study (Silverman et al. 2012)

Nested case-control study with 198 lung cancer deaths and 562 incidence density – sampled control subjects. To each case up to four control subjects were selected, individually matched on:

- Mining facility
- Sex
- Race/ethnicity
- Birth year (within 5 years)

Data collection on smoking history, education, occupational history, medical history, family medical history, and diet

Employment in other high-risk occupations

Duration	Cases	Controls	OR (95%-CI)
No	100	365	1.0 (referent)
0 to <5y	24	90	0.90 (0.52 – 1.55)
5 to <10y	6	53	0.49 (0.19 - 1.21)
≥10y	39	68	1.75 (1.06 - 2.91)
Unknown	29	90	1.14 (0.67 - 1.92)

[Silverman et al. 2012, table 1]

Causes of death:

Pneumoconiosis (N=17): 1 Silicosis, 1 Asbestosis, 15 other pneumoconiosis

Other pneumoconiosis – Surface only: N=3; SMR= 6.13 (95%CI: 1.26 - 17.91)
Ever-underground: N=12; SMR=16.21 (95%CI: 8.37 - 28.32)

Further adjustment

- Further adjustment for

  a.) history of employment in high-risk occupations for lung cancer (2 parameters)

  b.) history of respiratory disease (2 parameters)

- Adjustment for **cross-classified categories** of **smoking status / smoking intensity / work location** (15 parameters)

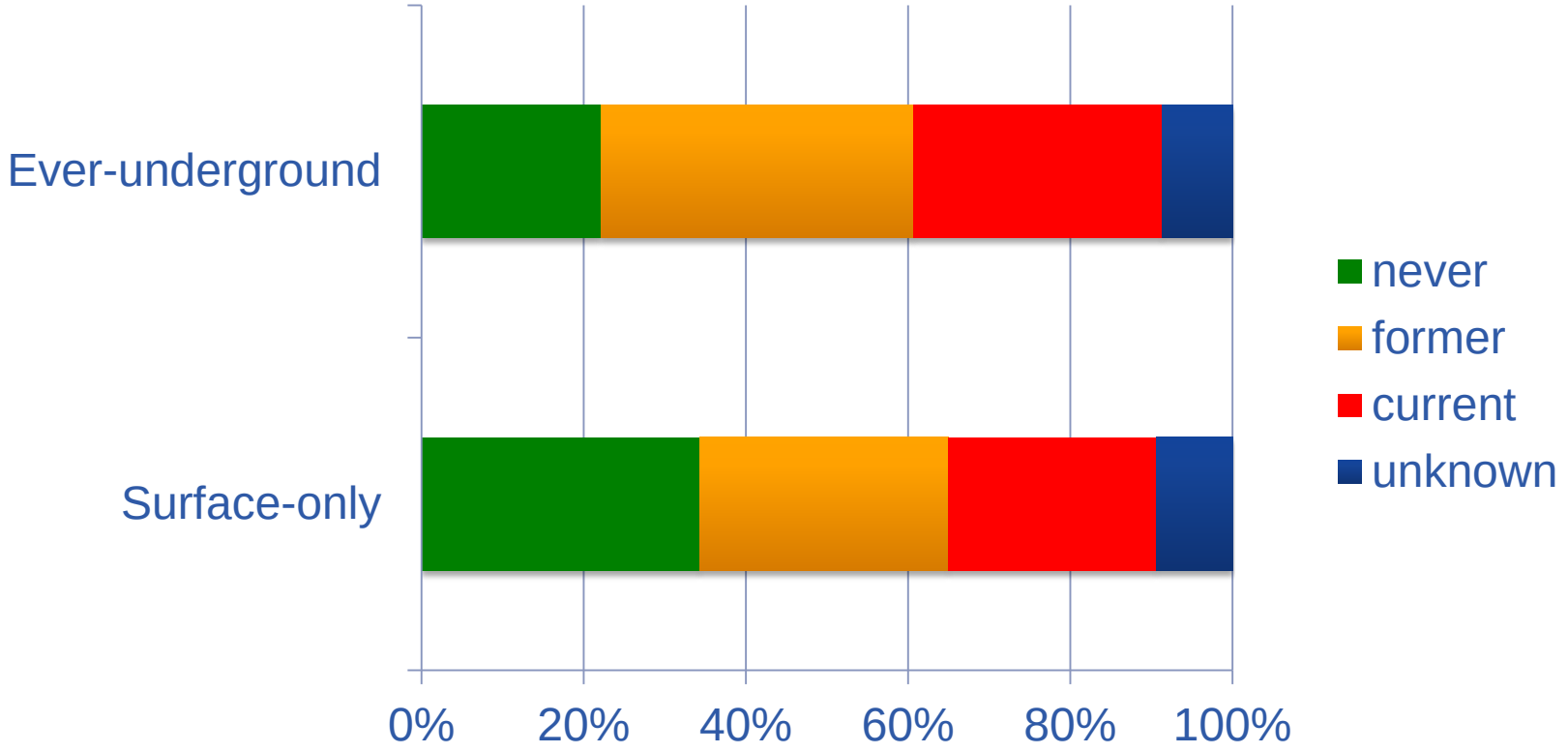
Results of the case-control analysis

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for average and cumulative REC and total duration REC exposure*

Exposure metric	Case subjects	Control subjects	OR (95% CI)
Cumulative REC, quartiles, unlagged, μg/m³-y			
0 to <19	49	151	1.0 (referent)
19 to <246	50	214	0.87 (0.48 to 1.59)
246 to <964	49	147	1.50 (0.67 to 3.36)
≥964	50	154	1.75 (0.77 to 3.97)
Quartiles, lagged 15 y, μg/m³-y			
0 to <3	49	158	1.0 (referent)
3 to <72	50	228	0.74 (0.40 to 1.38)
72 to <536	49	157	1.54 (0.74 to 3.20)
≥536	50	123	2.83 (1.28 to 6.26)

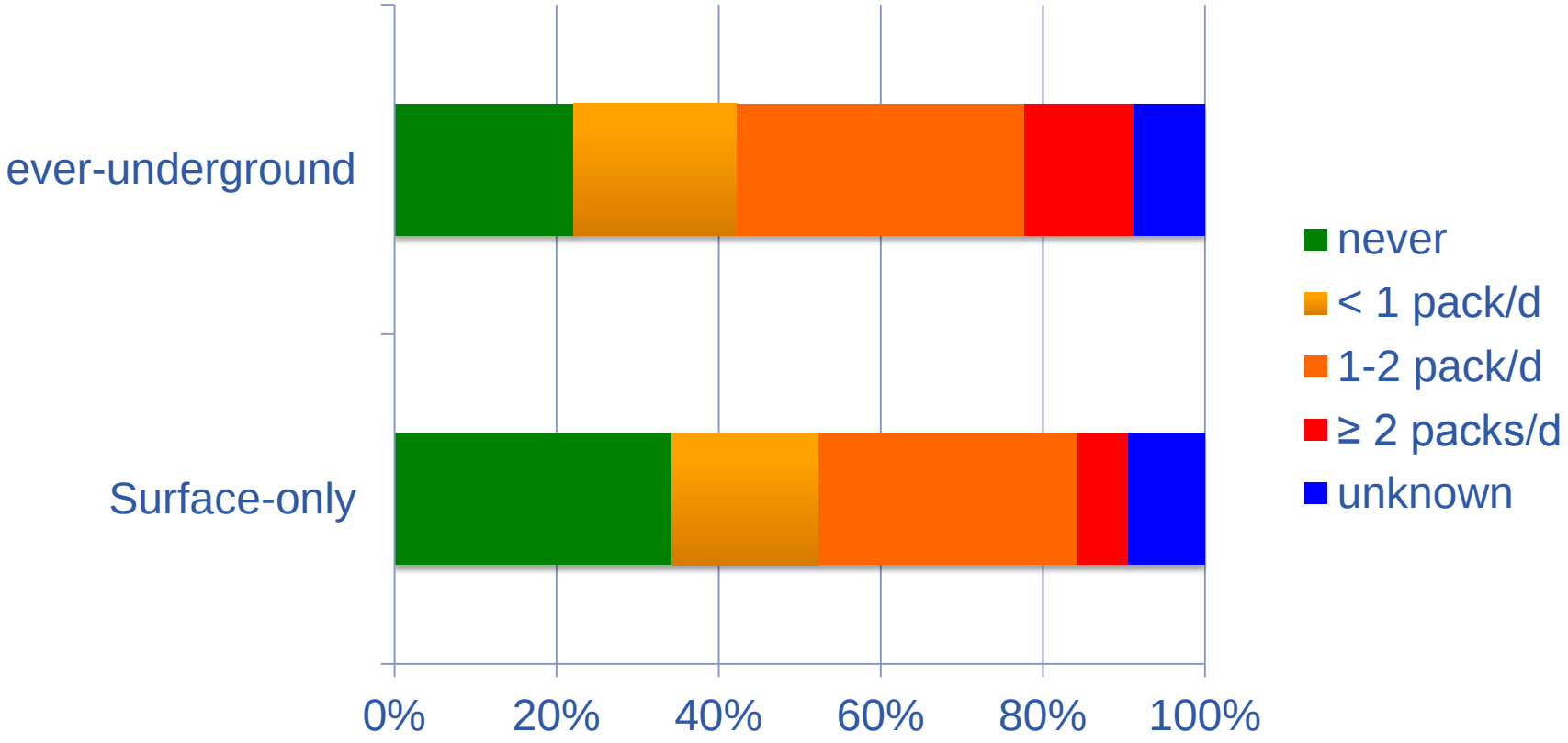
* *P* values based on two-sided Wald test for linear trend; adjusted for smoking status/mine location combination (surface work only/never smoker, surface work only/unknown/occasional smoker, surface work only/former smoker/<1 pack per day, surface work only/former smoker/1 to <2 packs per day, surface work only/former smoker/≥2 packs per day, surface work only /current smoker/<1 pack per day, surface work only/current smoker/1 to <2 packs per day, surface work only/current smoker/≥2 packs per day, ever underground work/never smoker, ever underground work/unknown/occasional smoker, ever underground work/former smoker/<1 pack per day, ever underground work/former smoker/1 to <2 packs per day, ever underground work/former smoker/≥2 packs per day, ever underground work/current smoker/<1 pack per day, ever underground work/current smoker/1 to <2 packs per day, ever underground work/current smoker/≥2 packs per day); history of respiratory disease 5 or more years before date of death/reference date; and history of a high-risk job for lung cancer for at least 10 years. REC = respirable elemental carbon.

Smoking status – DEMS controls only



[Data from Silverman et al. 2012, Table 2]

Smoking intensity – DEMS controls only



[data from Silverman et al. 2012, table 2]

Validity of information on lung cancer cases from next-of-kin

- About 85 % of case subjects had died > 10 years before interview [range of year of death: 1948 – 1997]
- Information mostly comes from adult children (55%)
- Share of missing information

Smoking:	8.6%	[10.7% (controls)]
Respiratory disease:	29.3%	[21.2%]
Family history of lung cancer:	13.6 %	[10.0%]

Conclusions

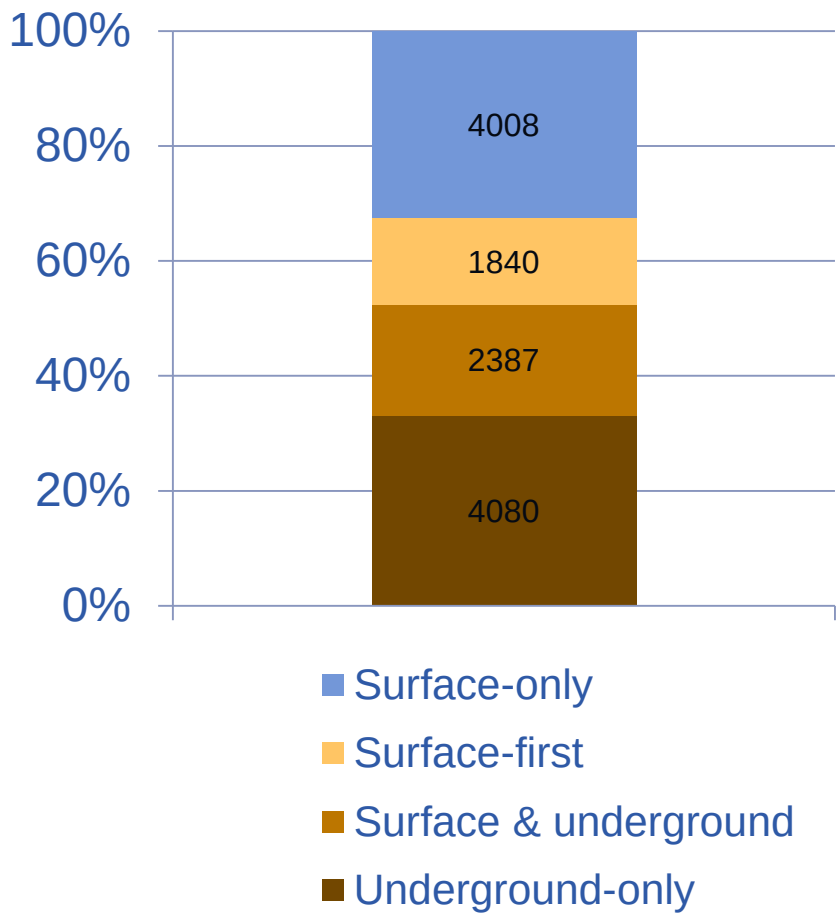
- The validity of the data on smoking seems to be low, especially with respect to the timescale of smoking.
- All analyses should be repeated with crude adjustment for smoking (ever/never) and without adjustment for smoking.

Critical evaluation of the DEMS results

Ever-underground vs. surface-only workers
(own calculation)
Data taken from table 2 [Silverman et al, 2012]
Unconditional logistic regression

OR = 1.03 (95%CI: 0.74 – 1.43) – crude odds ratio
OR = 0.92 (95%CI: 0.66 – 1.30) – smoking adjusted (8 cat.)

DEMS-Cohort by work location



Surface-first

- 22% of ever-underground workers
- Better health status in comparison to surface-only workers ?

Critical evaluation of the DEMS results

- Some results contradict to DEMS investigators conclusions: *Ever-underground* workers have had higher REC exposure and smoked more than *surface-only* workers and their SMR is lower.
- The results of the a-priori-defined case-control analyses should be disclosed.
- If an interaction between smoking and underground work is to be taken into account, this must depend on the duration of underground work.
- As a second classification of workers by work location they should be classified into surface-first and underground-first workers.

The current state of the DEMS analysis does not provide any evidence for an exposure-response relationship between DEE and lung cancer risk

Cohort study in Trucking Industry Workers (Laden et al., 2007; Garshick et al., 2008, 2012)

- Cohort of 31,135 male workers employed in the unionized U.S. trucking industry in 1985
  ≥ 1 year of work in a trucking industry job
  ≥ 40 years of age in 1985
- Mortality follow-up from 1985 until 2000 for lung cancer
- Exposure estimation for 8 job categories, JEM
- Mean age at hire = 36.0 (± 8.3) years
  Mean age in 1985 = 49.1 (± 6.0) years
- "*On average, workers were hired in their mid-30s, most likely due to hiring policies requiring previous experience*."

Statistical methods in the truckers study

- Cox model with attained age as time axis
- Ordinal variable for calendar year (1985-2000) to closely adjust for lung cancer secular trends
- Adjustment for race/ethnicity, census region
- Separate baseline hazards based on decade of hire (< 1960, 1960-9, 1970-9, ≥ 1980) and age in 1985 (40 to <50, 50 to <60, 60 to <70, ≥70 years)
- *Additional adjustment for years of employment in the unionized U.S. trucking industry*

Lung cancer Risk (Garshick et al., 2012, Table 4)

	Entire cohort (n = 31,135)		Cohort excluding mechanics (n = 29,324)	
Exposure	HR (95% CI) unadjusted for duration of work	HR (95% CI) adjusted for duration of work	HR (95% CI) unadjusted for duration of work	HR (95% CI) adjusted for duration of work
Cumulative EC (µg/m^3-months)				
No lag				
< 530	Reference	Reference	Reference	Reference
530 to < 1,061	1.13 (0.90, 1.42)	1.24 (0.98, 1.57)	1.13 (0.90, 1.42)	1.25 (0.99, 1.60)
1,061 to < 2,076	1.14 (0.89, 1.47)	1.30 (0.99, 1.70)	1.13 (0.87, 1.46)	1.30 (0.99, 1.72)
≥ 2076	0.98 (0.74, 1.29)	1.16 (0.86, 1.57)	1.02 (0.76, 1.36)	1.24 (0.89, 1.71)
p for trend	0.37	0.92	0.63	0.71
5-year lag				
< 371	Reference	Reference	Reference	Reference
371 to < 860	1.18 (0.92, 1.51)	1.30 (1.01, 1.68)	1.18 (0.92, 1.52)	1.31 (1.01, 1.71)
860 to < 1,803	1.16 (0.88, 1.53)	1.35 (1.01, 1.81)	1.17 (0.88, 1.55)	1.38 (1.02, 1.87)
≥ 1,803	1.12 (0.83, 1.52)	1.36 (0.98, 1.89)	1.19 (0.86, 1.63)	1.48 (1.05, 2.10)
p for trend	0.97	0.39	0.61	0.16

Lung cancer hazard per 1,000 µg/m³-months (5-year lag): HR = 1.07 (95%CI: 0.99, 1.15)

Main methodological problems in the truckers study

- Pre-exposure to DEE in former jobs
- Exclusion of mechanics
- Adjustment for years of employment

Dieselization in the U.S. trucking industry

Table 1. Distribution of jobs in 1985 among men ≥ 40 years of age with ≥ 1 year of work (n = 31,135).

Job in 1985	Job duties	n (%)
Long-haul driver (LH)	Drives heavy-duty trucks between large terminals. Diesel first used 1951–1957; transition complete 1954–1965, depending on company	10,825 (35)
Pick-up/delivery (P&D)	Drives trucks locally; picks up and delivers cargo. Diesel first used 1972–1978; transition complete 1980–1992, depending on company	5,866 (19)
Dockworker	Loads/unloads cargo on dock using forklifts Diesel forklifts in three companies starting in 1979–1986 through 1994–1996 in large terminals	5,710 (18)
Combination worker	Duties include P&D driver and dockworker	4,938 (16)
Mechanic	Maintains trucks in large terminal shops	1,741 (6)
Hostler	Drives a tractor or a specialized tractor to move trailers to and from freight dock and in yard	666 (2)
Clerk	Cashiers, dock clerks, dispatchers, customer service representatives, and others in terminal offices	843 (3)
Other jobs	Janitor, unionized manger, trainee, or not defined	546 (2)

Some facts on long-haul truck drivers

	L-H drivers (2010)	2010 NHIS
Diabetes	14.4 %	6.8 %
Obese (BMI ≥ 30) Morbid obesity (BMI ≥ 40)	68.9 % 17.4 %	30.5 % 7.3 %
Current cigarette smoker	50.7 %	18.9 %
Not covered by health insurance	38.1 %	17.2 %

Number of days sleeping at home in past 30 days	Number of respondents (%)
0 days	250 (18.3)
1-6 days	558 (44.6)
≥ 7 days	456 (37.1)
Don‘t know/refused/missing	1 (0.02)

Data from the National Survey of U.S. Long-Haul Truck Driver Health and Injury; Sieber et al., 2014

Pre-exposure to DEE in former jobs

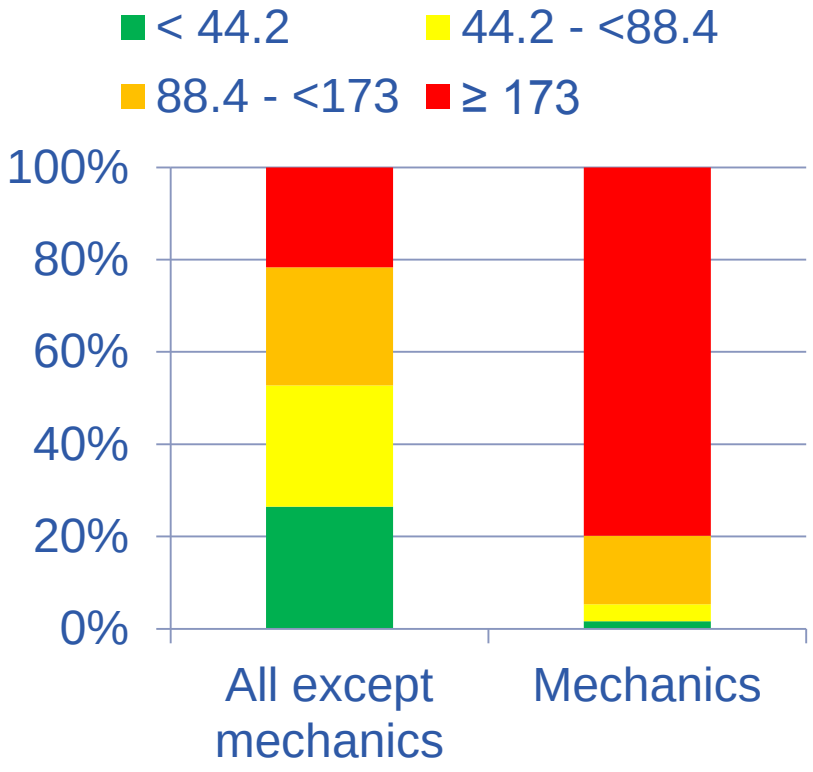
Do separate baseline hazards based on decade of hire and age in 1985 help to control the impact of pre-exposure to DEE in former jobs?

NO!

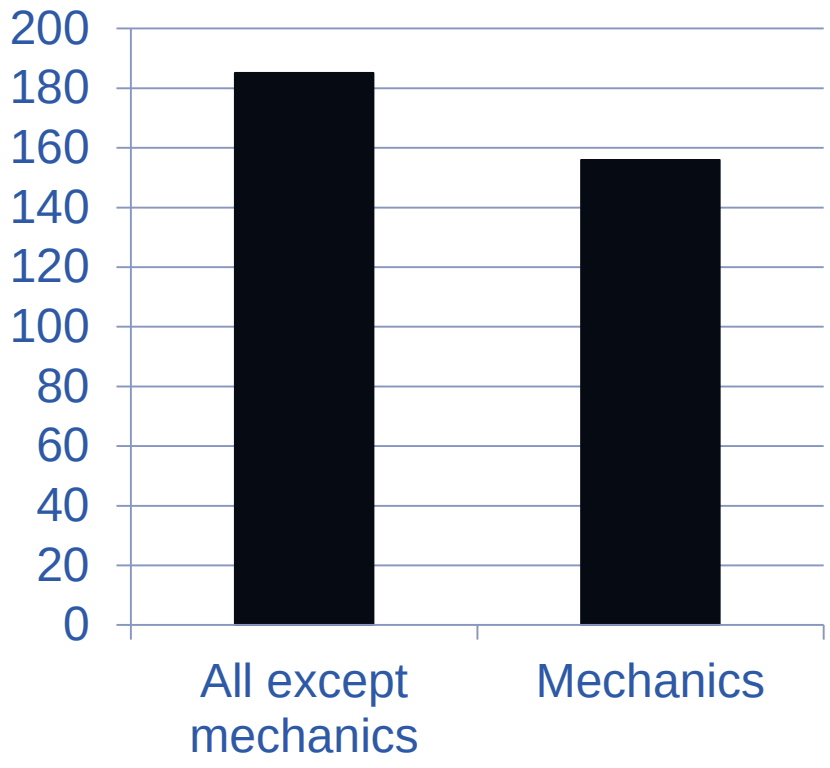
Because of the special demands and strains in the job as long-haul truck driver (family, lifestyle), it seems unlikely that someone will switch to this job.

Comparison of mechanics with other jobs

Cumulative REC-exposure (µg/m³-years)



Crude mortality rate for lung cancer



Garshick et al., 2012, Table 4

Age in 1985:	49.1	49.4

Adjustment for years of employment

- Duration of employment was correlated with cumulative REC; r = 0.55 – 0.74 (depending on lag)
  HR = 0.97 (95%CI: 0.96 – 0.99) per year of work
- Duration of employment take into account only the time in the companies included in the study.
- Health reasons for termination of the job are mainly the loss of the license due to obesity and related conditions like diabetes (Thiese et al., 2015).
- A lag time of 5 (or 10) years is sufficient to adjust for medical conditions, related to the later lung cancer

Final conclusions

- The lung cancer risk due to DEE/REC exposure seems to be overestimated in the two studies
- A re-analysis of the DEMS is recommended
- The 2 studies on underground miners yield comparable results

  [SMR for lung cancer in the German study is 0.73]
- The SMR for lung cancer in the trucker cohort is 1.04 (Laden, 2007), what is low in view of the smoking habits in LH drivers.

References

1. Heinrich et al (1995) Inhal Toxicol **7**: 533-556 [10.3109/08958379509015211]
2. Liang et al (2005) J Environ Monit **7**(10):983-988 [10.1039/b504728e]
3. Laden et al (2007) Environ Health Perspect **115**(8): 1192-6 [10.1289/ehp.10027]
4. Garshick et al (2008) Environ Health Perspect **116**(10): 1327-32 [10.1289/ehp.11293]
5. Attfield et al (2012) JNCI **104**(11):869-83 [10.1093/jnci/djs035]
6. Silverman et al (2012) JNCI;**104**(11):855-68 [10.1093/jnci/djs034]
7. Boffetta (2012) JNCI **104**(23): 1842-3 [10.1093/jnci/djs416]
8. Möhner et al (2012) JNCI **104**(23): 1846-7 [10.1093/jnci/djs423]
9. Garshick et al (2012) Environ Health Perspect **120**(9): 1301-6 [10.1289/ehp.1204989]
10. Möhner et al (2013) Eur J Epidemiol **28**(2): 159-68 [10.1007/s10654-013-9784-0]
11. IARC (2014). Arsenic, Metals, Fibres and Dusts. IARC Monographs Vol. 105
12. Holford et al (2014) Am J Prev Med **46**(2): e31-37 [10.1016/j.amepre.2013.10.022]
13. Vermeulen et al (2014) Environ Health Perspect 122(2): 172-7 [10.1289/ehp.1306880]
14. Sieber et al (2014) Am J Ind Med **57**(6): 615-26 (10.1002/ajim.22293)
15. HEI (2015). Health Effects Institute, Special Report 19
16. Thiese et al (2015) J Occup Environ Med **57**(6): 659-65 (10.1097/JOM.0000000000000422)
17. Möhner (2016) Eur J Epidemiol **31**(8): 803-4 [10.1007/s10654-016-0161-7]
18. Silverman et al (2016) Eur J Epidemiol **31**(8): 805-6 [10.1007/s10654-016-0188-9]
19. Möhner & Wendt (2017) Crit Rev Toxicol **47**(3): 185-224 [10.1080/10408444.2016.1266598]
20. Silverman (2018) Am J Epidemiol **187**(6): 1149-52 [10.1093/aje/kwy036]
21. Chang et al (2018) Am J Epidemiol **187**(6): 1210-9 [10.1093/aje/kwy038]
22. Möhner (2018) Eur J Epidemiol **33**(12): 1251-4 [10.1007/s10654-018-0455-z]
23. Möhner (2019) Am J Epidemiol **188**(2): 184-5 [10.1093/aje/kwy166]
24. Chang et al (2019) Am J Epidemiol **188**(2): 489-91 [10.1093/aje/kwy176]
25. Silverman (2019) Am J Epidemiol **188**(2): 486-7 [10.1093/aje/kwy168]

Thank you for your attenti

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