Is diesel equipment in the workplace safe or not?

Roel Vermeulen, PhD

IRAS, Environmental Epidemiology Division
Utrecht University, the Netherlands

Julius Center, Health Sciences and Primary Care
University Medical Center Utrecht, The Netherlands

Universiteit Utrecht

Outline

- Hazard identification
  - Animal and mechanistic data
  - Epidemiological evidence
- Risk characterization
  - Exposure-response
  - Burden
- Conclusion & Outlook

Hazard identification I

IARC monograph, Vol 46, 1988

- There is limited evidence for the carcinogenicity in humans of diesel engine exhaust.
- There is sufficient evidence for the carcinogenicity in experimental animals of whole diesel engine exhaust.

EVIDENCE IN HUMANS	EVIDENCE IN EXPERIMENTAL ANIMALS: *Sufficient*	*Limited*	*Inadequate*	*ESLC*
Sufficient	Group 1			
Limited	↑1 strong evidence in exposed humans Group 2A	↑2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A Group 2B (exceptionally, Group 2A)		
Inadequate	↑1 strong evidence in exposed humans ↑2A strong evidence … mechanism also operates in humans Group 2B ↓3 strong evidence … mechanism does not operate in humans	↑2A belongs to a mechanistic class ↑2B with supporting evidence from mechanistic and other relevant data Group 3	↑2A belongs to a mechanistic class ↑2B with strong evidence from mechanistic and other relevant data Group 3	Group 3 ↓4 consistently and strongly supported by a broad range of mechanistic and other relevant data
ESLC	Group 3			Group 4

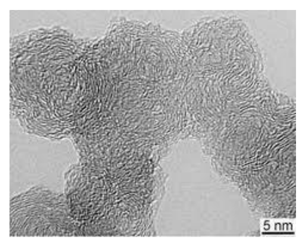
Hazard Identification – Limitations in epidemiological data

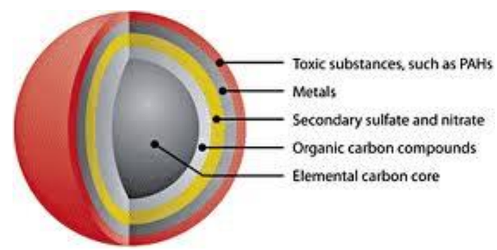
- Lack of control for confounding
  - Smoking
- Insufficient (quantitative) exposure assessment
- Lack of exposure -response associations within and across occupations

IARC monograph, Vol 105, 2012 Animal and Mechanistic Evidence

The Working Group concluded that there was:

- “sufficient evidence” in experimental animals for the carcinogenicity of whole diesel-engine exhaust, of diesel-engine exhaust particles, and of extracts of diesel-engine exhaust particles.





- “strong evidence” for the ability of whole diesel-engine exhaust to induce cancer in humans through genotoxicity.
  - Bulky DNA adducts, Chromosomal damage, oxidative stress etc.

Universiteit Utrecht

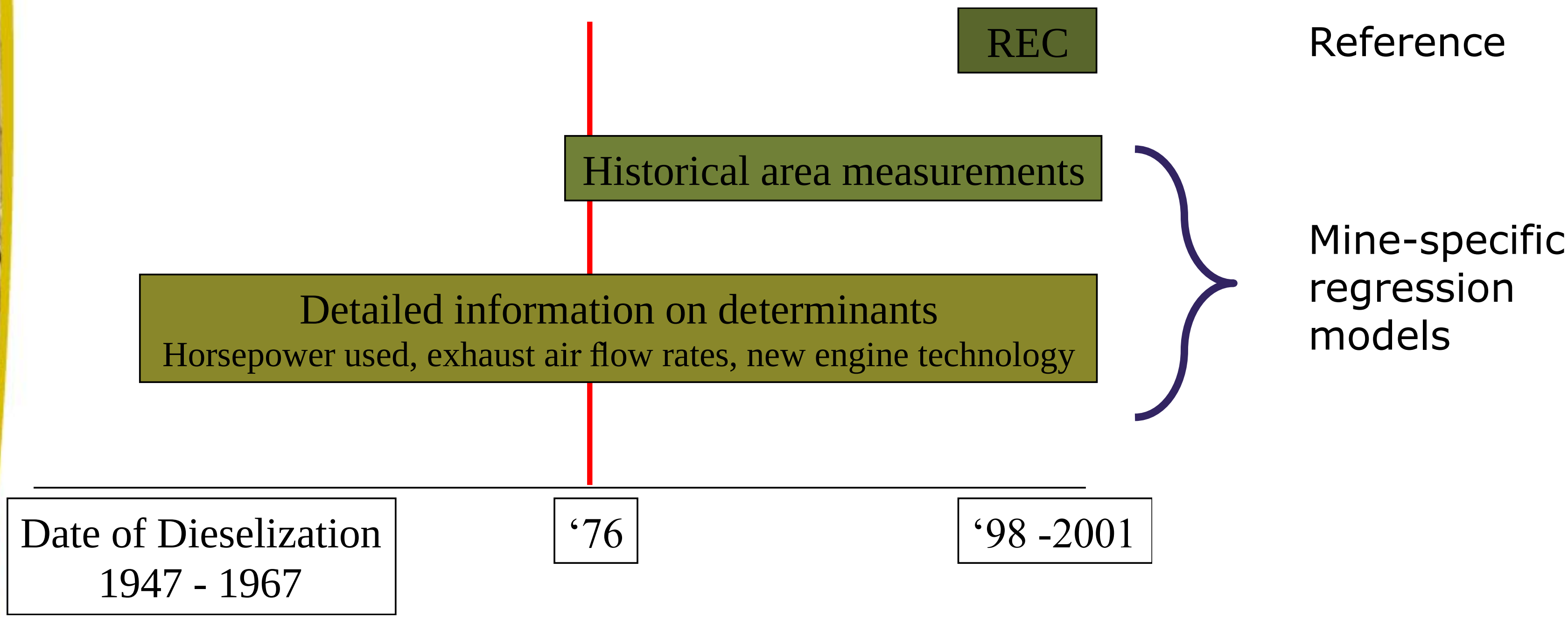
IARC monograph, Vol 105, 2012
Epidemiological Evidence

- Several new studies were conducted to address the previously noted short-comings
  - *Lack of control for confounding*
    - *Smoking*
  - *Insufficient (quantitative) exposure assessment*
  - *Lack of exposure -response associations*

The NCI/NIOSH project
Diesel Exhaust in Miners Study (DEMS)

- 8 US **non-metal** mining facilities (i.e. Trona, Salt, Potash)
- 12,315 blue-collar workers
- Mean yrs 8.0 underground (n=8,307)
- First diesel use 1947 – 1967
- Mortality assessment through 1997 (50 yrs)
- Nested case-control study
    - 198 lung cancer cases and 611 matched controls
    - Next-of-kin interview (smoking, other jobs)
- Extensive exposure assessment
    - Diesel exhaust
    - silica, asbestos, radon (negligible)

Estimation of Historical DE Exposure Levels Underground



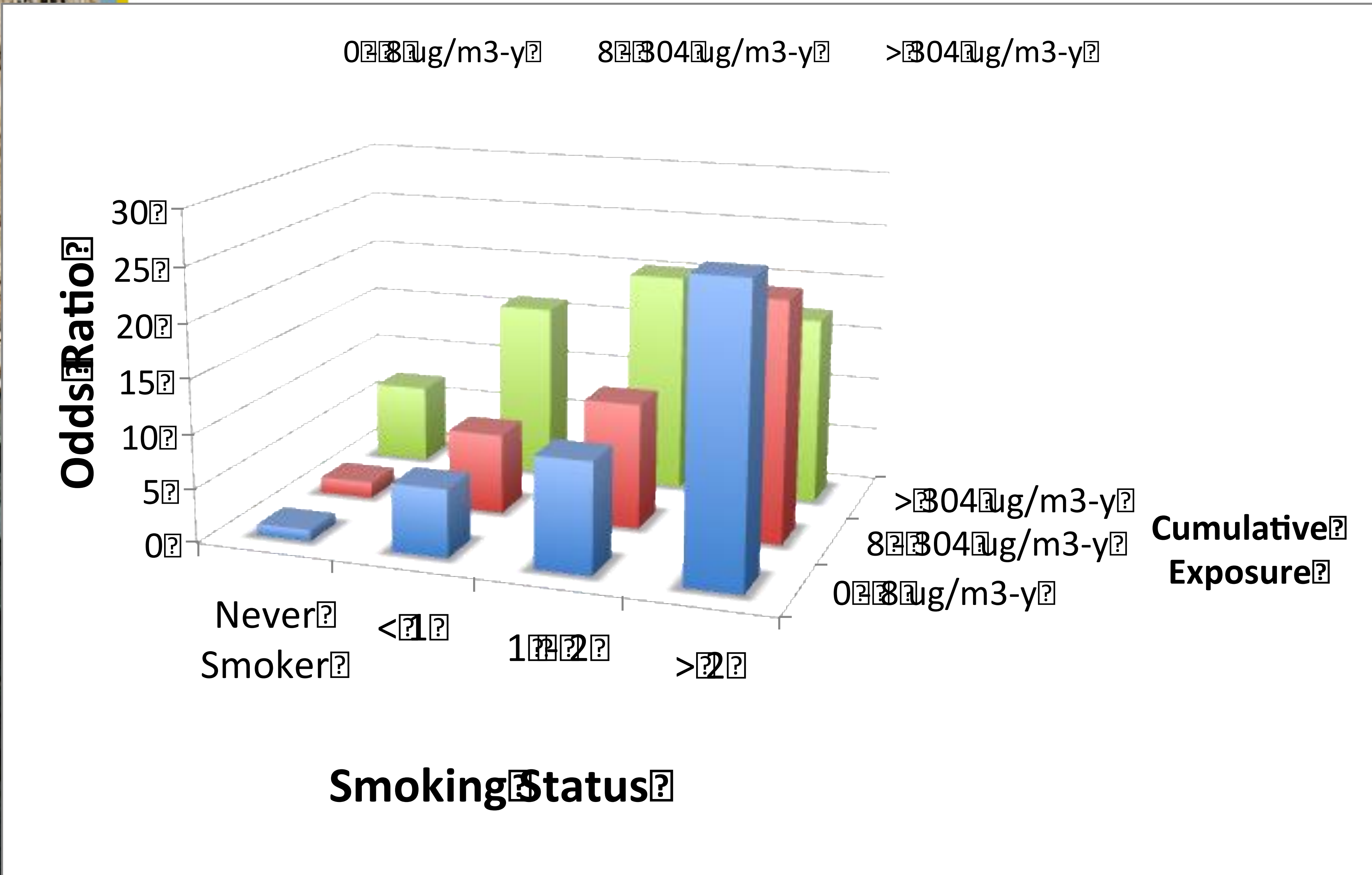
Underground Miner Lung Cancer Mortality

COHORT *Cumulative $\mu g/m^3$-yr	0 to < 108	108 to <445	445 to < 946	≥946
cases	30	31	30	31
Hazard Ratio	1.00	1.50 0.86 - 2.62	2.17 1.21 - 3.88	2.21 1.19 - 4.09
CASE-CONTROL Cumulative $\mu g/m^3$-yr	**0 to < 81**	**81 to <325**	**325 to < 878**	**≥878**
cases	29	29	29	29
Odds Ratio	1.00	2.46 1.01 - 2.46	2.41 1.00 – 5.82	5.10 1.88- 23.87

***Below 1280 $\mu g/m^3$-yr risk is linear ($p=0.001$)**

Case-control data adjusted for smoking, respiratory disease history, previous work in job at high risk for cancer.

Odds Ratio for cumulative REC exposure by smoking intensity



US Trucking Industry (Garshick et al., 2012)

- Retrospective cohort study
  - 54,319 make unionized trucking company workers
  - Employed in 1985 in 4 US companies
- Mortality through 2000
- 779 lung cancer cases
- Analysis limited to 31,135 men with 1+ yrs of work
- Detailed exposure assessment

Lung cancer HRs associated with each quartile of cumulative EC exposure

Cumulative $\mu g/m^3$-yr	< 31	31 to < 72	72 to < 150	> 150
Cases	122	179	202	248
Hazard Ratio	1.00	1.31 (1.01 - 1.71)	1.38 (1.02 - 1.87)	1.48 (1.05 - 2.10)

*Analyses corrected for tenure excluding mechanics

IARC monograph, Vol 105, 2012
Diesel engine exhaust and lung cancer

- The findings of the new cohort studies were supported by those in other occupational groups and by case–control studies including various occupations involving exposure to diesel-engine exhaust.

Universiteit Utrecht

Hazard Identification – Limitations in epidemiological data

- ✓ Lack of control for confounding
  - ✓ Smoking
- ✓ Insufficient (quantitative) exposure assessment
- ✓ Lack of exposure -response associations within and across occupations

Universiteit Utrecht

Is diesel equipment in the workplace safe or not?

IARC monograph, Vol 105, 2012
Summary Hazard identification

- There is sufficient evidence for the carcinogenicity in humans of diesel engine exhaust. Diesel engine exhaust causes lung cancer. Also, a positive association between diesel engine exhaust and bladder cancer has been observed.

- There is sufficient evidence for the carcinogenicity in experimental animals of whole diesel engine exhaust.

Overall evaluation

- Diesel engine exhaust is carcinogenic to humans (Group 1).

Universiteit Utrecht

Outline

- Hazard identification
  - Animal and mechanistic data
  - Epidemiological evidence

- Risk characterization
  - Exposure-response
  - Burden

Research

All EHP content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1306880.

Exposure-Response Estimates for Diesel Engine Exhaust and Lung Cancer Mortality Based on Data from Three Occupational Cohorts

Roel Vermeulen,[1] Debra T. Silverman,[2] Eric Garshick,[3] Jelle Vlaanderen,[1,4] Lützen Portengen,[1] and Kyle Steenland[5]

[1]Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands; [2]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA; [3]Pulmonary and Critical Care Medicine Section, Medical Service, Veterans Affairs Boston Healthcare System; Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [4]Section of Environment and Radiation, International Agency for Research on Cancer, Lyon, France; [5]Department of Environmental and Occupational Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

Risk Characterisation

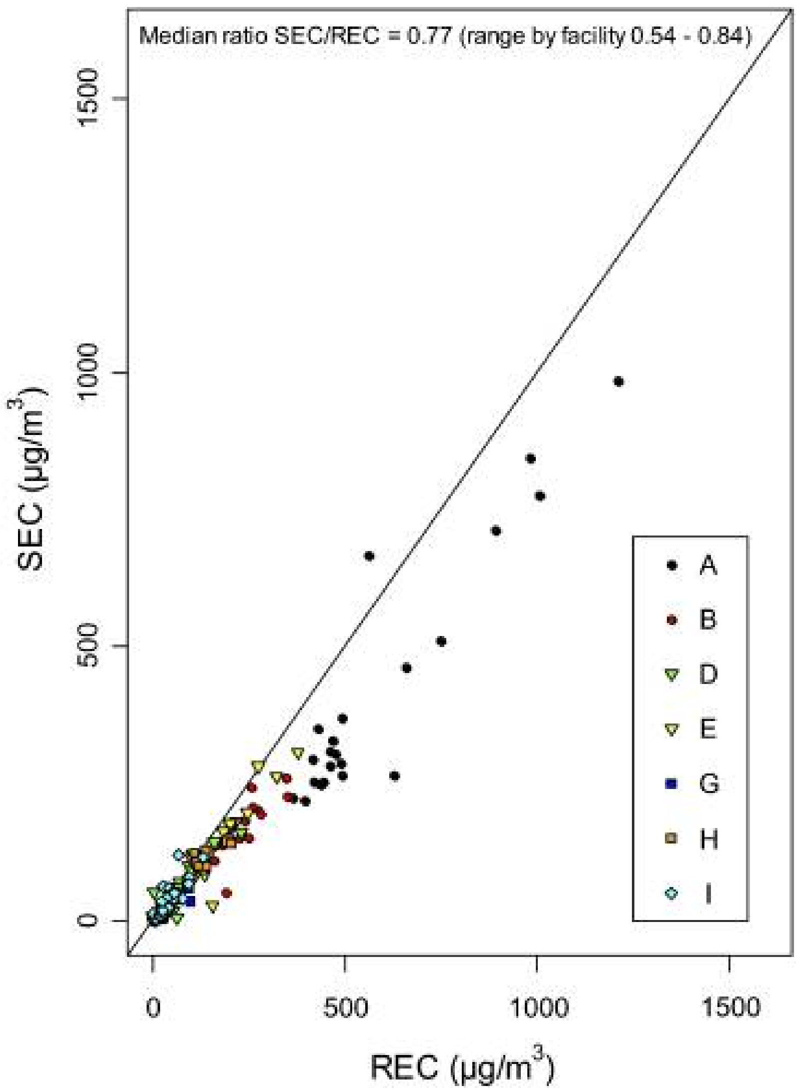
- At the time of the IARC evaluation, three US occupational cohort studies of cumulative exposure to elemental carbon (EC; a marker of DEE) and lung cancer mortality had reported exposure-response estimates:
  - A study of non-metal miners (198 lung cancer deaths) (*Silverman et al. 2012*)
  - Two independent studies of trucking industry workers (779 and 994 lung cancer deaths, respectively) (*Garshick et al. 2012; Steenland et al. 1998*).
  - *A fourth cohort study of potash miners (68 lung cancers) with EC exposure-response data was published after the IARC evaluation (Mohner et al. 2013)*.

Combining the Available Diesel and Lung Cancer Mortality Studies

Can the endpoints and exposures be combined?

- Endpoints
  - Lung cancer mortality
- Risk models
  - Relative risk models
  - Lagged models (5 – 15yrs)
- Diesel exhaust exposure
  - NIOSH 5040 method to measure EC
  - Size-fraction (SEC vs. REC)
  - Diesel fuel sources contribution to EC

SEC to REC comparison DEMS study



Median SEC/REC ratio = 0.77
At low exposures around x=y

No correction

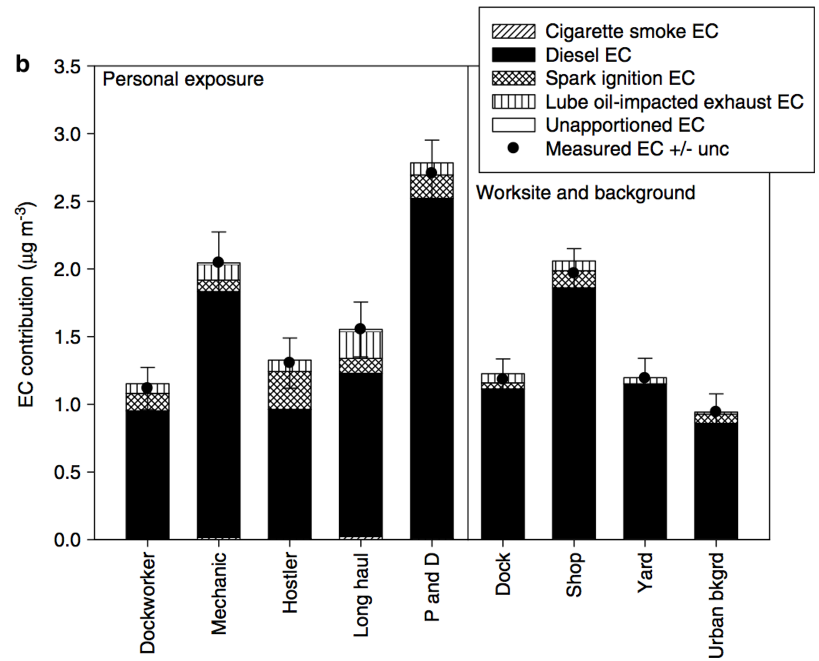
- Single survey
- Little difference between SEC and REC based on mass
- Most particles are in the submicron size

Truckers study: Estimated median SEC/REC ratio = 0.90 - 0.95
[Personal communication T. Smith]

Vermeulen et al., 2010

Source Apportionment EC

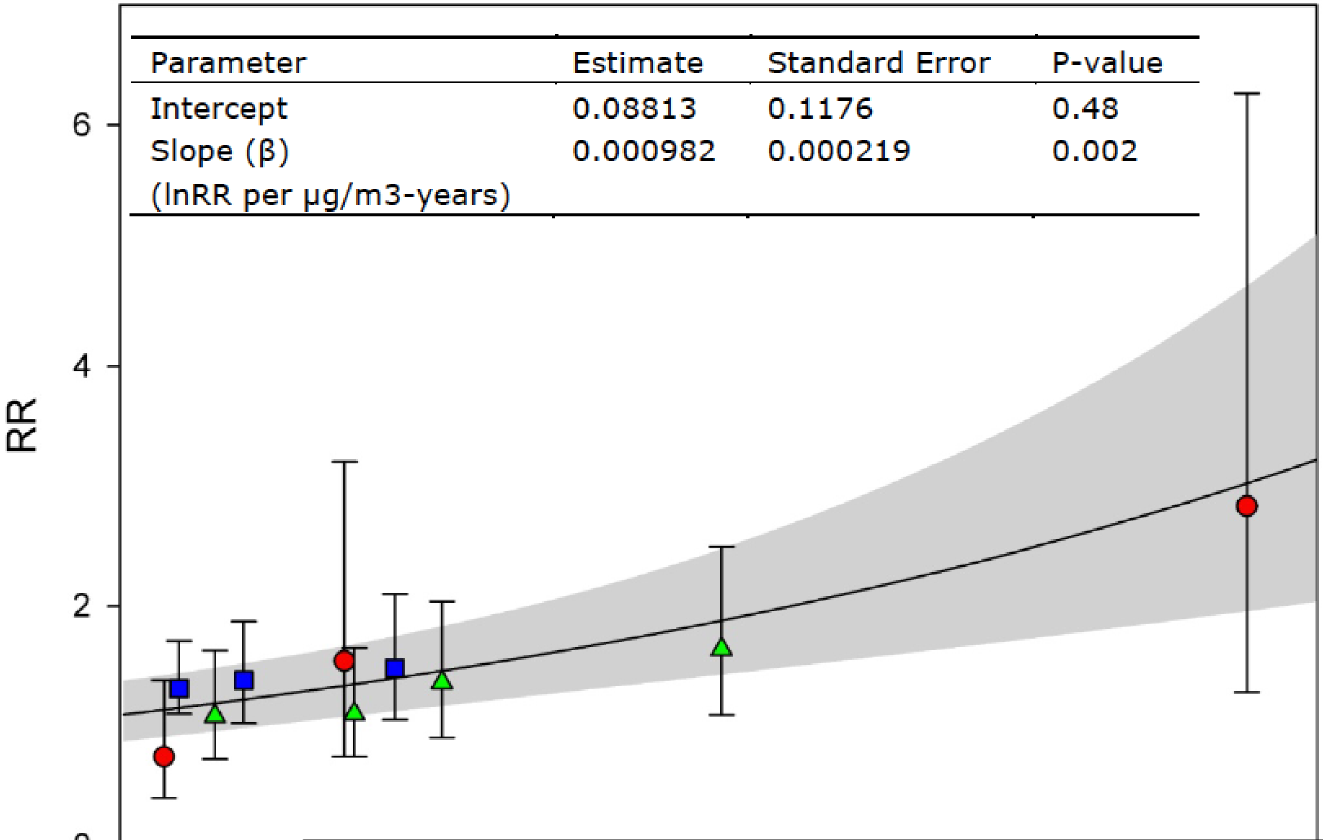
- DEMS study: ~100% Diesel fueled sources
- Garshick / Steenland: ~90% Diesel fueled sources
  - median 91% (min:max 0.73 – 0.97)



Sheesley et al., 2008

Universiteit Utrecht

Exposure –response DEE and Lung Cancer Risk



Parameter	Estimate	Standard Error	P-value
Intercept	0.08813	0.1176	0.48
Slope (β) (lnRR per µg/m3-years)	0.000982	0.000219	0.002

Model[a]	β	(95%CI)
Silverman et al. (2012) only	0.0012	(0.00053, 0.00187)
Steenland et al. (1998) only	0.00096	(0.00033, 0.00159)
Garshick et al. (2012) only	0.00061	(-0.00088, 0.00210)

Universiteit Utrech

Exposure –response DEE and Lung Cancer Risk

Perspectives | Correspondence

All EHP content is accessible to individuals with disabilities. Fully accessible (Section 508–compliant) HTML versions of these articles are available at http://dx.doi.org/10.1289/ehp.1408482 and http://dx.doi.org/10.1289/ehp.1408482R.

The correspondence section is a public forum and, as such, is not peer-reviewed. EHP is not responsible for the accuracy, currency, or reliability of personal opinion expressed herein; it is the sole responsibility of the authors. EHP neither endorses nor disputes their published commentary.

Meta-Analysis of Lung Cancer Risk from Exposure to Diesel Exhaust: Study Limitations

http://dx.doi.org/10.1289/ehp.1408482

Vermeulen et al. (2014) published a meta-

Vermeulen et al. (2014) predicted an OR of 5.5, and my model predicted an OR of 2.17). Similar results were obtained using a 0-year lag (5-year and 0-year were the only lag data to which we had access).

Meta-Analysis of Lung Cancer Risk from Exposure to Diesel Exhaust: Vermeulen et al. Respond

http://dx.doi.org/10.1289/ehp.1408482R

Crump asserts that we "inappropriately mixed data from exposures lagged 5 years and 15 years" in our study published in *Environmental Health Perspectives* (Vermeulen et al. 2014). Exposure metrics

Morfeld and Spallek *Journal of Occupational Medicine and Toxicology* (2015) 10:31
DOI 10.1186/s12995-015-0073-6

RESEARCH

Diesel engine exhaust and
risks – evaluation of the m
Vermeulen et al. 2014

Peter Morfeld[1,2*] and Michael Spallek[3,4]

– Therefore, the results of the meta-regression analysis by Vermeulen et al. [1] should not be used in a risk assessment without reservation, especially not in the low-DEE exposure range.

- Choice of studies
- Choice of risk estimates
- Choice of lag-times
- Choice of model

} Uncertainty

Universiteit Utrecht

Exposure –response DEE and Lung Cancer Risk

Workplace

SHORT REPORT

Is diesel equipment in the workplace safe or not?

Roel Vermeulen, Lützen Portengen

- Re-analyses of the ERC based on
  - Original analyses published by Vermeulen et al. N=1
  - Sensitivity analyses published by Vermeulen et al. N=2-9
  - Alternative (published) ERCs N=10-14

Universiteit Utrecht

Exposure –response DEE and Lung Cancer Risk

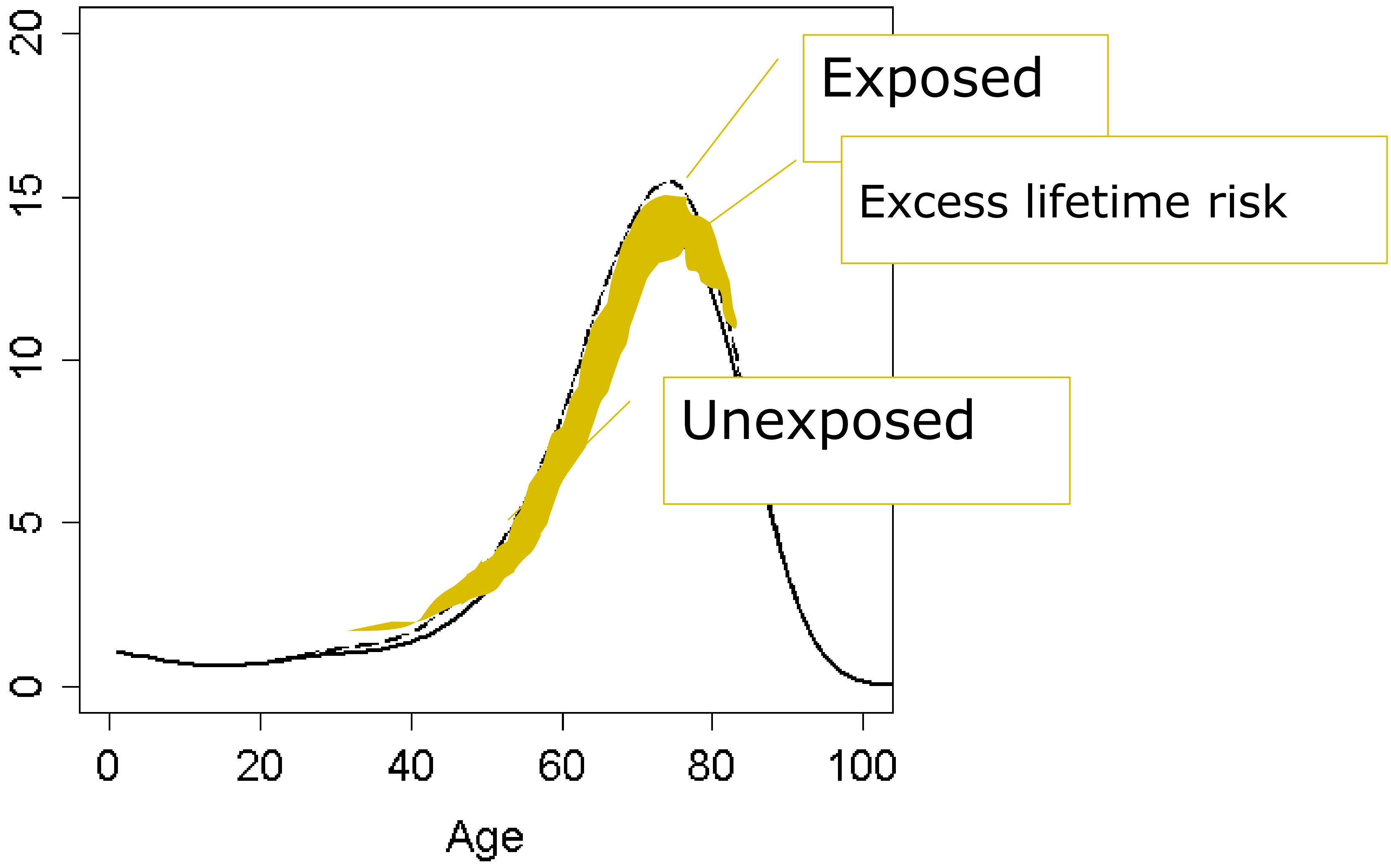
Serial number	Contributing studies and selected analyses			ERC slope factor (lnRR per μg/m³ years)
	Garshick *et al*	Silverman *et al*	Steenland *et al*	
1	*5 years lag; excl mechanics*	*15 years lag*	*5 years lag*	0.000982

Range ERC Slope factor: 0.000605 – 0.001181

Quantitative Risk Assessment

- Selection of ERC [# 1-14]
- Selection of acceptable risk
  - lifetime excess cumulative risk of dying from DME at:
  - Acceptable risk: 10^{-6} per exposure year (40 years tenure: 4 to 10^{-5})
  - Maximum tolerable risk: 10^{-4} per exposure year (40 years tenure: 4 to 10^{-3})
- Life-table analysis
  - To estimate the excess risk of dying from lung cancer due to DME by contrasting lung cancer mortality in a hypothetical population with no or only background exposure to that in a population where everybody was exposed according to a specific DME scenario
    - Hypothetical birth cohort of 10 000 participants till age 120
    - Time − varying incidence rate: $\lambda(x,t) = \lambda_0(t) * \exp(\beta * x)$
    - Exposure duration of 40 years (age 20 – 60)
    - Excess risk calculation truncated at the age of 100

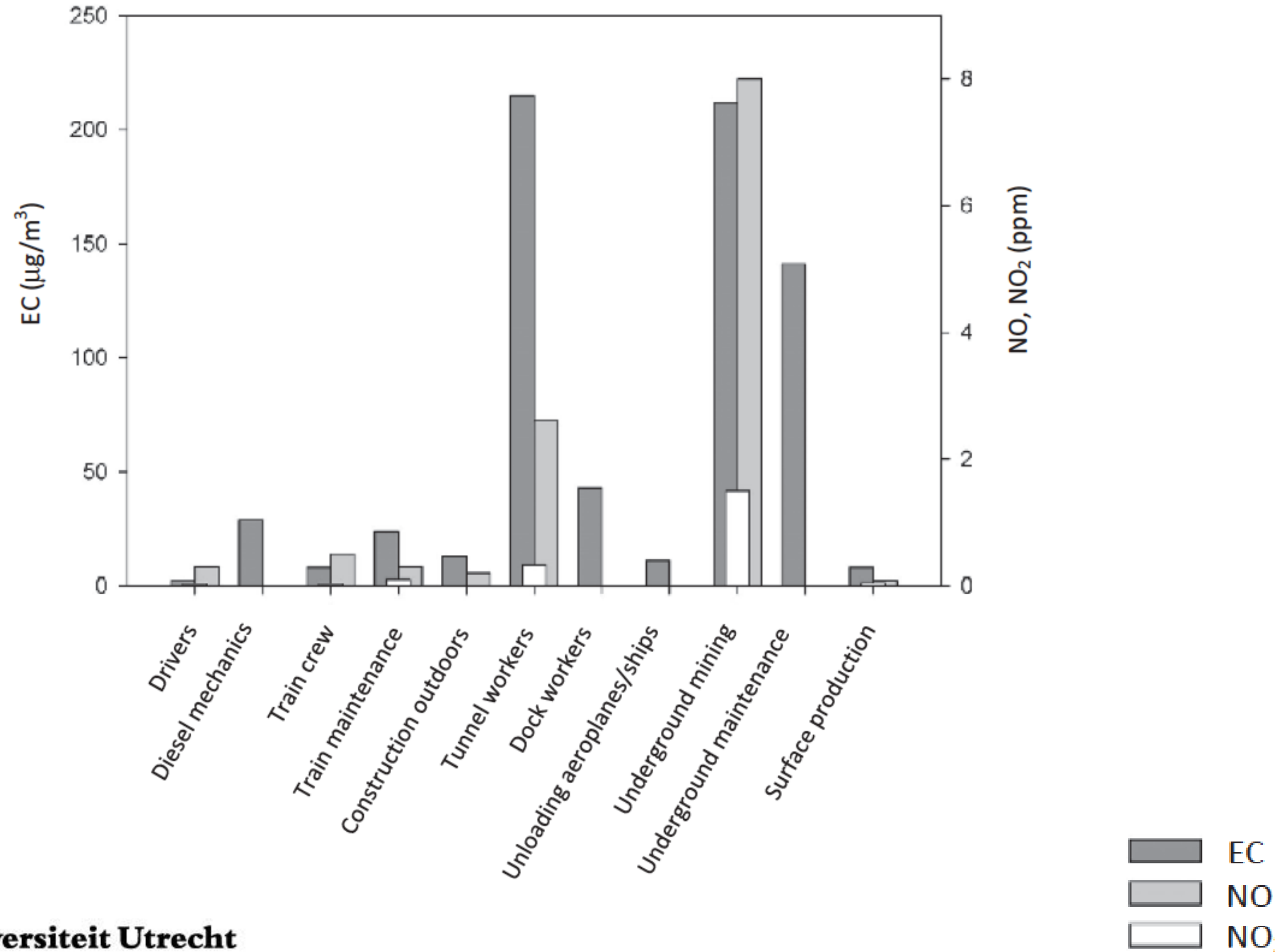
Lifetable analyses



Quantitative Risk Assessment

Serial number	ERC slope factor (lnRR per μg/m^3 years)	Acceptable risk (4 to 10^{-5}) EC (μg/m^3)	MTR (4 to 10^{-3}) EC (μg/m^3)
1	0.000982	0.011	1.03
2	0.000909	0.011	1.11
3	0.001021	0.010	0.99
4	0.000936	0.011	1.08
5	0.000608	0.017	1.66
6	0.001060	0.010	0.95
7	0.000927	0.011	1.09
8	0.000646	0.016	1.56
9	0.000713	0.015	1.42
10	0.000774	0.013	1.30
11	0.001066	0.010	0.95
12	0.001181	0.009	0.85
13	0.000959	0.011	1.05
14	0.000605	0.017	1.67

Average personal exposures to elemental carbon by major occupational groups



Universiteit Utrecht

Is diesel equipment in the workplace safe or not?

Although there is uncertainty in the exact ERC, the implications of the QRA are not

Is diesel equipment in the workplace safe or not?

Is it practical to set an OEL for DME?

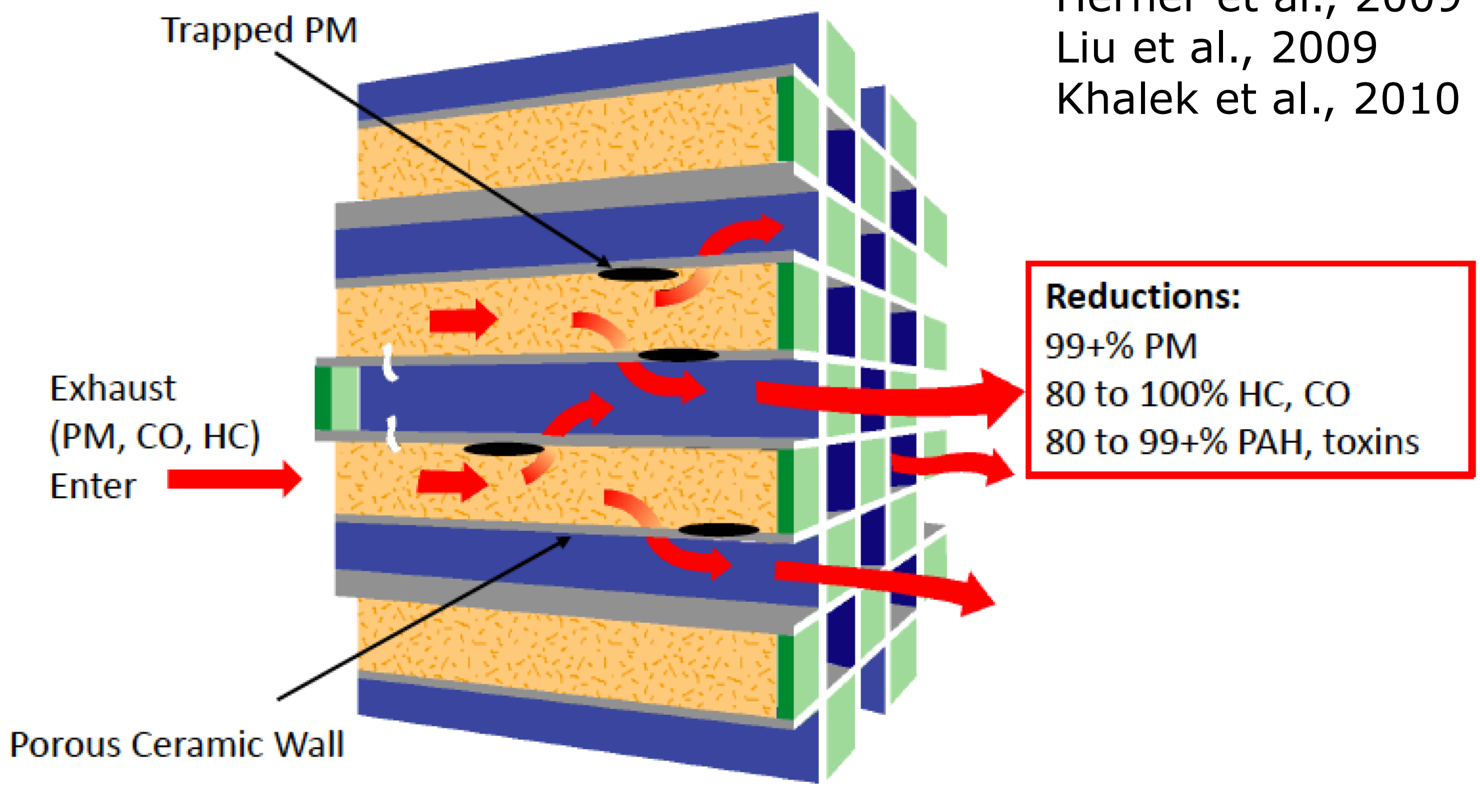
Practical considerations of setting an exposure limit for DME

- Acceptable risk < environmental level
- Maximum tolerable risk ~ urban environmental levels

- Elemental carbon might be a good marker of exposure for traditional diesel but not for new technology diesel engine (NTDE)

New Technology Diesel Engine (NTDE) Reduces Emissions Across a Broad Spectrum of Compounds

Herner et al., 2009
Liu et al., 2009
Khalek et al., 2010



The potential benefits of particulate matter reduction using a catalyzed DPF may be confounded by increases in NO_2 emission and release of reactive ultrafine particles (Karthikeyan et al., 2013)

Conclusion and outlook

- Diesel engine exhaust causes lung cancer.
- Available studies to date with an exposure response association between DEE (as measured by EC) and lung cancer mortality show a robust association.
- Results of QRA show that AR and MTR levels are respectively 0.01 and 1.0 ug/m^3 EC.
- These levels are below many contemporary occupational (environmental) exposure situations.
- NTDE technology will likely reduce emissions. However, before NTDE will have penetrated into the off-road diesel engine market this will likely still take many years.
- (Practical) **Occupational exposure limits should be set for diesel and efforts should be taken to move to an expedited process of removal of older technology diesel (non-NTDE) from the workplace.**

Acknowledgements

NCI
- Debra Silverman
- Patricia Stewart
- Joseph Coble
- Jay Lubin
- Aaron Blair
- Claudine Samanice
- Sholom Wacholder

NIOSH
- Michael Attfield
- Patricia Schleiff
- Daniel Yereb
- Rebecca Stanevich

Utrecht University
- Lutzen Portengen
- Jelle Vlaanderen

Harvard Medical School
- Eric Garshick

Emory University
- Kyle Steenland

Universiteit Utrecht