Overview of adverse health risks associated with diesel engine exhaust

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Conflicts of interest

- Member of DECOS of the Netherlands Health Council till first public draft of DME OEL draft (member of the DME subgroup)
- Member of the SCOEL of the EU (member of subgroup of DME opinion document, rapporteur of DME OEL draft document (completed but never published because of an expired mandate)
- Member of the Environmental Health Committee of the European Respiratory Society as ERS officer (chair epidemiology and environment assembly)
- Independent member of the Committee for Chemical Agents of the Socio-Economic Council of the Netherlands
- Co-opted member RAC-ECHA
- Not involved in DME health effects related research projects

Outline

- Diesel exhaust exposure and population at risk
- Health effects & mechanisms
- Epidemiology
- Exposure response studies

Kauppinen et al 2000, HazChem@work

- Population at risk in EU28: Diesel exhaust 3.000.000 occupationally exposed individuals

- Truck and lorry drivers, ferry and dock workers, mechanics, construction workers, miners, etc.

Diesel exhaust composition

Average emissions from US 2004 compliant (corresponding to EU 1998–2000) and US 2007 compliant (corresponding to EU 2013/Euro VI) heavy-duty diesel engines (taken from NEG 2016).			
Compound	US 2004 (EU 1998–2000) compliant engines (average ± SD, mg/h)	US 2007 (EU 2013) compliant engines (average ± SD, mg/h)	Reduction of emissions (%)
Elemental carbon	3 445 ± 1 110	23 ± 4.7	99
Organic carbon	1 180 ± 71	53 ± 47	96
Inorganic ions	320 ± 156	92 ± 38	71
Metals and elements	400 ± 141	6.7 ± 3.0	98
PAHs	325 ± 106	70 ± 24	79
Nitro-PAHs	0.3 ± 0.0	0.1 ± 0.0	81
Single-ring aromatics	405 ± 149	72 ± 33	82
Alkanes	1 030 ± 240	155 ± 78	85
Hopanes/steranes (polycyclic hydrocarbons)	8.2 ± 6.9	0.1 ± 0.1	99
Alcohols and organic acids	555 ± 134	107 ± 25	81
Carbonyls	12 500 ± 3 536	255 ± 95	98
Dibenzodioxins and furans	nd	$6.2 \times 10^{-5} \pm 5.2 \times 10^{-5}$	nd

‘old’ ‘new’ diesel exhaust

Acute toxicity (from SCOEL/Opin/403)

- Acute irritation
- Inflammatory and respiratory symptoms (e.g., eye, throat, lung) (cough, phlegm)
- Pulmonary inflammation in humans (challenge studies)
- Neurophysiological symptoms (e.g., light headedness, nausea)
- Immunological effects – exacerbation of allergenic responses to known allergens, increased sensitization risk
- Exacerbations of asthma
- Cardiovascular effects

Respiratory inflammation in humans

Effects observed around 100 µg DEEE/m^3 , 0.2 – 0.4 ml/m^3 NO_2 for 1 – 2 hours

Study subjects	Exposures	Concentrations	Effects	Reference
23 healthy, 32 asthmatics (mild to moderate), non-smokers, 15 min ergometer 15 min rest (20 l/min/m^2)	DEP [µg/m^3] NO_2 [ml/m^3] NO [ml/m^3] CO [ml/m^3] EC idling 1991 Volvo diesel engine (Volvo TD45, 4.5 l, four cylinders, 680 rpm)	100 (PM_{10}) 0,4 1,3 9,4 no data	18 h after exposure bronchoscopy: healthy: BW: neutrophils ↑, IL-6 ↑, myeloperoxidase ↑, No changes: IL-8, adhesion molecules (ICAM-1, P-+ E-selectin,, VCAM-1, stem cell-factor), GSH, GSSG asthmatics: PEF ↓ (8%), 24 h: PEF ↓ (14%), n.s. after 42 h, no other effects	Behndig et al. 2011

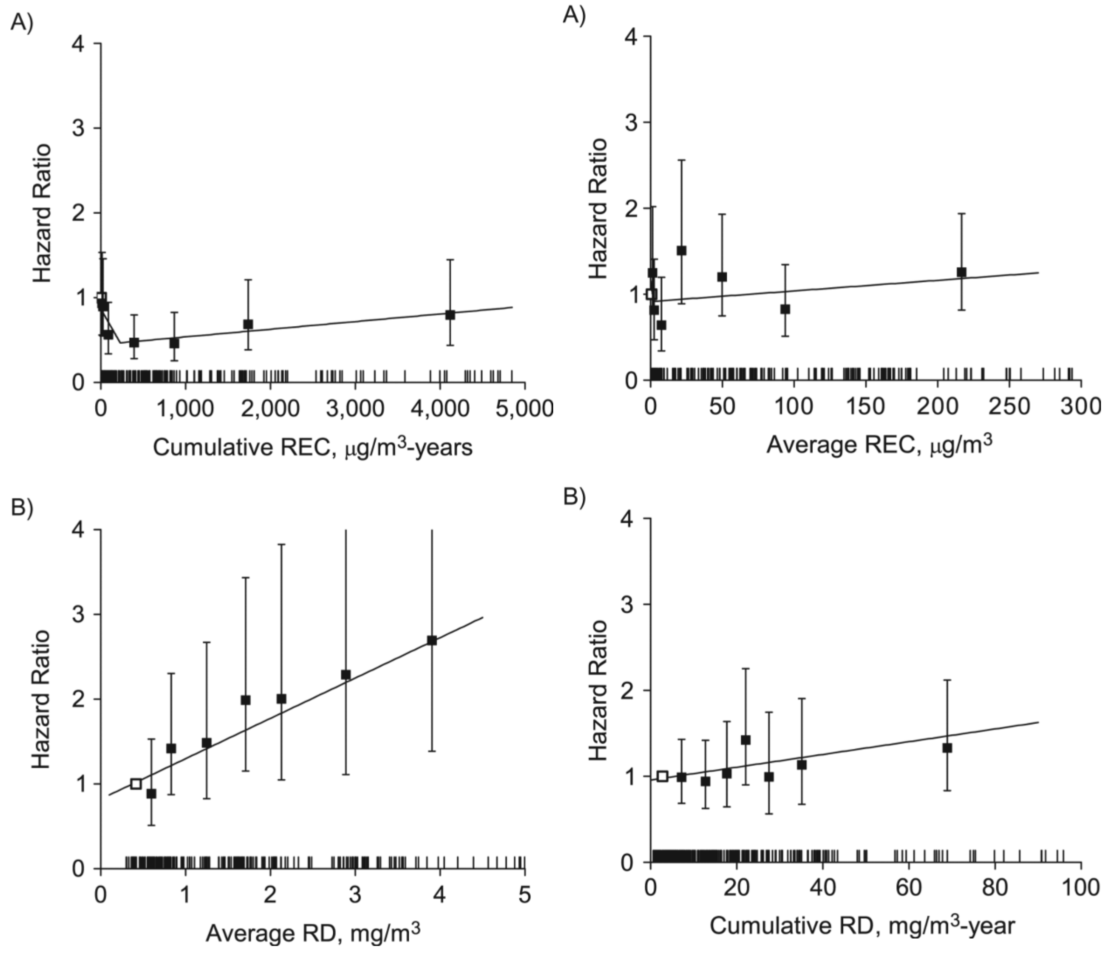
Most studies explored the nature of the inflammatory response

Single exposure level

No exposure response

Effects after repeated exposure

- Chronic inflammation
- Reduction of lung function (spirometry)
- Increased cardiopulmonary mortality
  - ischemic heart disease (several earlier studies, clear positive study by Costello et al., Am J Epid 2018 using respirable elemental carbon and respirable dust levels in 10799 US miners)



Carcinogenic properties

• IARC evaluation 1988	possible carcinogen (Group 2A)
• IARC evaluation 2012	human carcinogen (Group 1)

• Lung cancer	sufficient evidence
• Bladder cancer	limited evidence

Mode of Action

- IARC 2013 … concluded that *“there is strong mechanistic evidence that diesel engine exhaust can induce lung cancer in humans through genotoxic mechanisms including DNA damage, gene and chromosomal mutation, changes in relevant gene expression, the production of ROS and inflammatory responses. In addition, the co-carcinogenic, cell-proliferative and/or tumour-promoting mechanisms probably contribute to the lung carcinogenesis induced by diesel exhaust.”*

Mode of Action

- SCOEL …., there is evidence of a direct genotoxic activity as well as for indirect genotoxicity. Therefore,…., traditional DEE could be classified as category B ("*genotoxic carcinogen, for which the existence of a threshold cannot be sufficiently supported*")
- Or C ("*genotoxic carcinogen for which a practical threshold is supported*") carcinogen. "*Toxicological and pathobiological information from animal studies supports a mode of action, for which possibly a threshold could be established.*
- *However, the epidemiological evidence does not allow to identify a critical threshold that could serve for derivation of an OEL …*

Epidemiology: meta-analysis

Lipsett & Campleman, 1999

- 30 of 47 studies included
- Factors consistent with higher study quality were associated with higher risk estimates (adjustment for smoking, ↓ likelihood of selection bias, ↑ power)
- Pooled RR-estimate 1.47 (1.29-1.67)

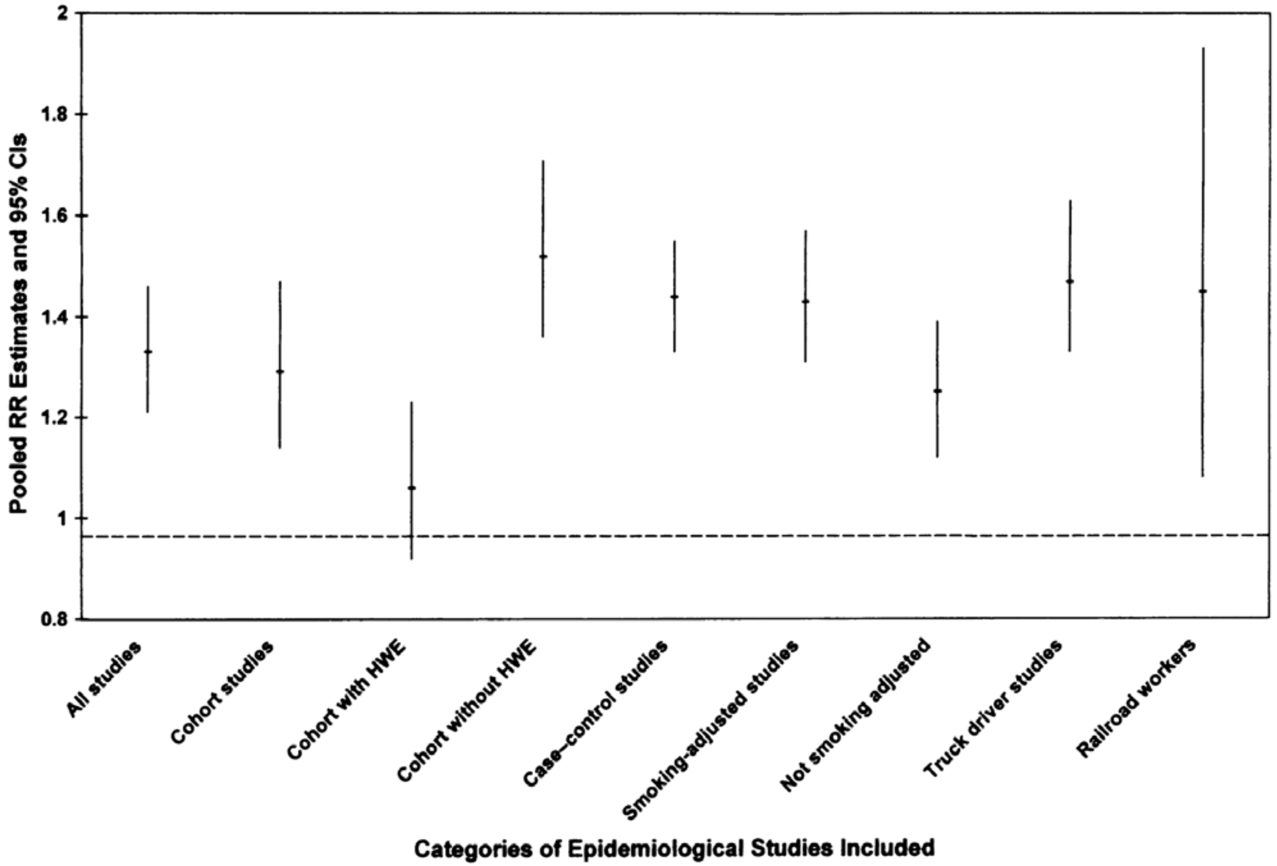
TABLE 1—Studies Included in Meta-Analysis of Diesel Exhaust Exposure and Lung Cancer

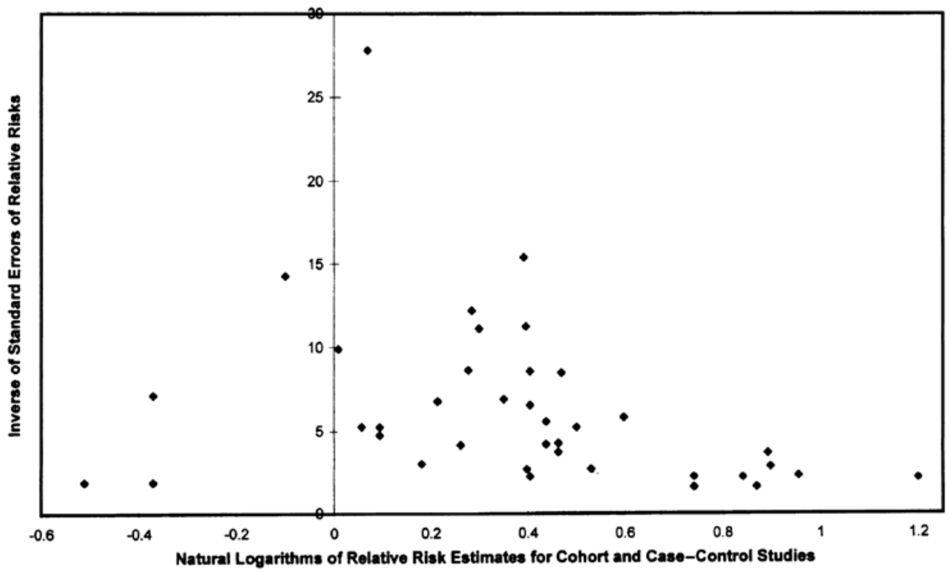
Study (Year)	Design	Location	Occupation or Exposure Group	Smoking Adjusted	No. of Lung Cancer Cases	RR	95% CI
Ahlberg et al. (1981)[16]	Cohort	Europe	Truck drivers	No	154	1.33	1.13, 1.56
Balarajan and McDowall (1988)[17]	Cohort	Europe	Truck drivers	No	280	1.59	1.00, 2.53[a]
Bender et al. (1989)[18]	Cohort	North America	Highway maintenance	No	54	0.69	0.52, 0.90
Benhamou et al. (1988)[19]	Case–control	Europe	Professional drivers	Yes	128	1.42	1.07, 1.89
	Case–control	Europe	Mechanics	Yes	65	1.06	0.73, 1.54
Boffetta et al. (1988)[23]	Cohort	North America	Truck drivers	Yes	48	1.24	0.93, 1.66
	Cohort	North America	Railroad workers	Yes	14	1.59	0.94, 2.69
	Cohort	North America	Heavy equipment operators	Yes	5	2.60	1.12, 6.06
Boffetta et al. (1990)[21]	Case–control	North America	Probable DE exposure ≥ 30 y	Yes	17	1.49	0.72, 3.11
Buiatti et al. (1985)[20]	Case–control	Europe	Transportation general	Yes	376	1.1	0.7, 1.6
Coggon et al. (1984)[24]	Case–control	Europe	DE-exposed group	No	32	1.1	0.7, 1.8
Damber and Larsson (1987)[14]	Case–control	Europe	Professional drivers	Yes	37	1.2	0.6, 2.2
Edling et al. (1987)[27]	Cohort	Europe	Bus drivers	No	5	0.69[b]	0.2, 1.6[b]
Garshick et al. (1987)[29]	Case–control	North America	Railroad workers ≥ 20 y[c]	Yes	117[f]	1.55	1.09, 2.21
Garshick et al. (1988)[30]	Cohort	North America	Railroad workers ≥ 15 y[c]	No	Not given	1.82	1.30, 2.55
Guberan et al. (1992)[31]	Cohort	Europe	Professional drivers	No	77	1.50	1.23, 1.81
Gustafsson et al. (1986)[32]	Cohort	Europe	Dock workers	No	70	1.32	1.05, 1.66
Gustavsson et al. (1990)[33]	Nested case–control	Europe	Bus garage workers[d]	No	15	1.49[d]	1.25, 1.77[d]
Hansen (1993)[35]	Cohort	Europe	Truck drivers	No	76	1.6	1.26, 2.0
Hayes et al. (1989)[36]	Case–control	North America	Truck drivers ≥ 10 y	Yes	112	1.5	1.1, 2.0
	Case–control	North America	Bus drivers ≥ 10 y	Yes	24	1.7	0.8, 3.4
	Case–control	North America	Mechanics (excluding auto) ≥ 10 y	Yes	18	2.1	0.9, 5.2
	Case–control	North America	Heavy equipment operators ≥ 10 y	Yes	10	2.1	0.6, 7.1
Howe et al. (1983)[37]	Cohort	North America	Railroad workers probably exposed	No	279	1.35	1.13, 1.61[a]
Lerchen et al. (1987)[15]	Case–control	North America	DE grouped	Yes	7	0.6	0.2, 1.6
Magnani et al. (1988)[41]	Death certificate study	Europe	DE grouped	No	379	0.97	0.94, 0.99
Menck and Henderson (1976)[43]	Cohort	North America	Truck drivers	No	109	1.65	1.13, 2.40[a]
	Cohort	North America	Mechanics (excluding auto)	No	46	3.32	1.35, 8.18[a]
Nokso-Koivisto and Pukkala (1994)[46]	Cohort	Europe	Railroad workers	No	230	0.90[d]	0.79, 1.04[d]
Pfluger and Minder (1994)[47]	Case–control	Europe	Professional drivers	Yes	284	1.48	1.30, 1.68
Rafnsson and Gunnarsdottir (1991)[49]	Cohort	Europe	Truck drivers ≥ 30 y	No	<24[f]	2.32	0.85, 5.04
Rushton et al. (1983)[50]	Cohort	Europe	Bus garage workers/mechanics	No	102	1.01	0.82, 1.22[b]
Siemiatycki et al. (1988)[52]	Case–control	North America	Diesel exhaust grouped	Yes	70	1.1	0.8, 1.5[e]
Steenland et al. (1990)[54]	Case–control	North America	Truck drivers ≥ 18 y	Yes	213	1.55	0.97, 2.47
	Case–control	North America	Truck mechanics ≥ 18 y	Yes	16	1.50	0.59, 3.40
Swanson et al. (1993)[55]	Case–control	North America	Heavy truck drivers ≥ 20 y	Yes	137	2.44[d]	1.43, 4.16[d]
	Case–control	North America	Railroad workers ≥ 10 y	Yes	49	2.46[d]	1.24, 4.87[d]
Wegman and Peters (1978)[57]	Case–control	North America	Transportation equipment operators	No	9	2.39[b]	0.71, 8.05[b]
Wong et al. (1985)[59]	Cohort	North America	Heavy equipment operators ≥ 20 y	No	163	1.07	1.00, 1.15[a]

Note. DE = diesel exhaust; RR = relative risk; CI = confidence interval.
[a]Calculated from *P* value.
[b]Calculated from data presented in publication.
[c]Risk estimates excluding shop workers.
[d]Pooled risk estimates from 2 racial or duration categories.
[e]90% confidence intervals originally presented within study.
[f]Exact number of cases for stratum analyzed not available.

Meta analysis

Lipsett & Campleman, 1999





Exposure studies review

Pronk et al., 2009

- Highest levels: enclosed underground work sites with heavy equipment (mining, mine maintenance, and construction) (EC 27–658 $\mu g/m^3$).
- Intermediate levels: above-ground (semi-) enclosed areas with smaller equipment (mechanics, emergency workers in fire stations, distribution workers at a dock, workers loading/unloading ferry terminals (EC <50 $\mu g/m^3$).
- Lowest levels enclosed areas: separated from source (drivers, train crew, or outside surface mining, parking attendants, vehicle testers, utility service workers, surface construction and airline ground personnel) EC<25 $\mu g/m^3$).

Synergy study coordinated by IARC

Olsen et al., 2011

- 13304 lung cancer cases
- 16282 controls
- From 11 cases control studies from Canada and Europe
- ISCO-68 occupational codes (no, low, high diesel exhaust exposure)

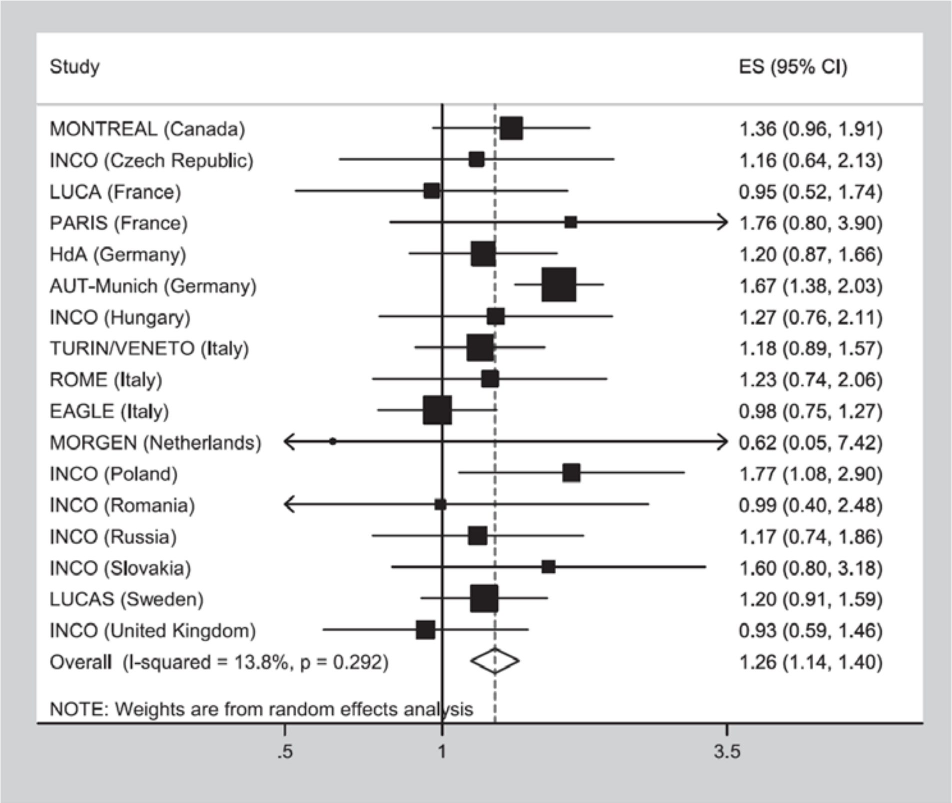


Figure 1. Study-specific odds ratios for the highest quartile of cumulative diesel motor exhaust exposure compared with never-exposed, adjusted for age, sex, cigarette pack-years, time-since-quitting smoking, and ever-employment in a "List A" job. CI = confidence interval; ES = odds ratio.

Synergy study

Olsen et al., 2011

TABLE 3. LUNG CANCER RISK ASSOCIATED WITH CUMULATIVE DIESEL MOTOR EXHAUST EXPOSURE

Subjects	Cumulative Diesel Motor Exhaust Exposure (*unit-years*)*	Cases	%	Controls	%	OR1[†]	95% CI	OR2[‡]	95% CI
All	Never	7,676	57.7	10,320	63.4	1.00	Reference	1.00	Reference
	<6	1,269	9.5	1,513	9.3	1.04	0.96–1.13	0.98	0.89–1.08
	6–17.33	1,325	10	1,497	9.2	1.13	1.04–1.23	1.04	0.95–1.14
	17.34–34.5	1,440	10.8	1,502	9.2	1.23	1.13–1.33	1.06	0.97–1.16
	>34.5	1,594	12	1,450	8.9	1.42	1.31–1.54	1.31	1.19–1.43
	Test for trend, P value					<0.01[§]		<0.01[§]	
Women	Never	2,144	86	2,810	86.4	1.00	Reference	1.00	Reference
	<6	146	5.9	198	6.1	0.85	0.68–1.07	0.83	0.64–1.08
	6–17.33	116	4.7	127	3.9	1.07	0.82–1.39	1.27	0.94–1.71
	17.34–34.5	51	2	71	2.2	0.87	0.60–1.26	0.94	0.62–1.42
	>34.5	35	1.4	45	1.4	1.03	0.66–1.63	1.58	0.96–2.59
	Test for trend, P value					0.83[§]		0.20[§]	
Never-smokers	Never	614	76.7	3,486	73	1.00	Reference	N/A	
	<6	44	5.5	334	7	0.74	0.52–1.05		
	6–17.33	63	7.9	328	6.9	1.22	0.90–1.65		
	17.34–34.5	33	4.1	305	6.4	0.85	0.57–1.26		
	>34.5	47	5.9	320	6.7	1.26	0.90–1.78		
	Test for trend, P value					0.28[§]			
Workers never employed in a "List A" job	Never	6,954	59.4	9,764	65	1.00	Reference	1.00	Reference
	<6	1,034	8.8	1,320	8.8	1.05	0.96–1.15	0.98	0.89–1.09
	6–17.33	1,091	9.3	1,309	8.7	0.15	1.06–1.26	1.07	0.97–1.18
	17.34–34.5	1,223	10.4	1,324	8.8	1.28	1.17–1.39	1.10	1.00–1.21
	>34.5	1,412	12.1	1,301	8.7	1.49	1.37–1.62	1.35	1.23–1.49
	Test for trend, P value					<0.01[§]		<0.01[§]	

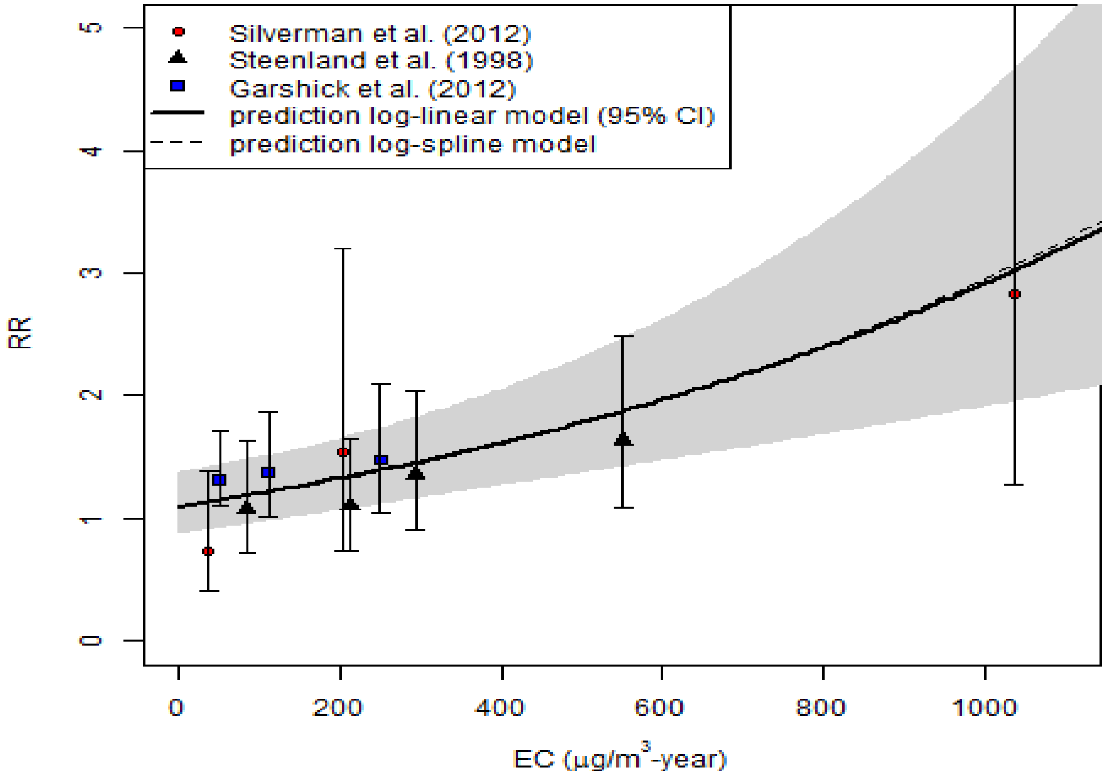
Definition of abbreviations: CI = confidence interval; OR = odds ratio.
* The categories represent the quartile distribution of cumulative diesel motor exhaust exposure among exposed controls.
† OR1 is adjusted for age, sex, study, and ever-employment in a "List A" job (*see* text for details).
‡ OR2 is additionally adjusted for pack-years and time-since-quitting smoking.
§ Test for trend, *P* value obtained using the continuous variable for cumulative exposure.

Quantitative exposure response studies

- Teamster Union Trucker study (Steenland et al., 1998): case-control study among workers in the US trucking industry (Central States Teamster Union)
- Trucker Industry Particle study (Garshick et al., 2012): US trucking industry workers was a retrospective cohort study
- Diesel Exhaust Mining Study (Attfield et al., 2012; Silverman et al., 2012, 2014): cohort & nested case-control study part of a large cohort mortality study of workers in the US non-metal mining industry (NCI, NIOSH)
- German Potash Study (Mohner et al., 2013): reanalysis of retrospective cohort study among nearly 6,000 German potash miners

Meta-analysis

Vermeulen & Portengen, 2014 and additional sensitivity analysis 2017



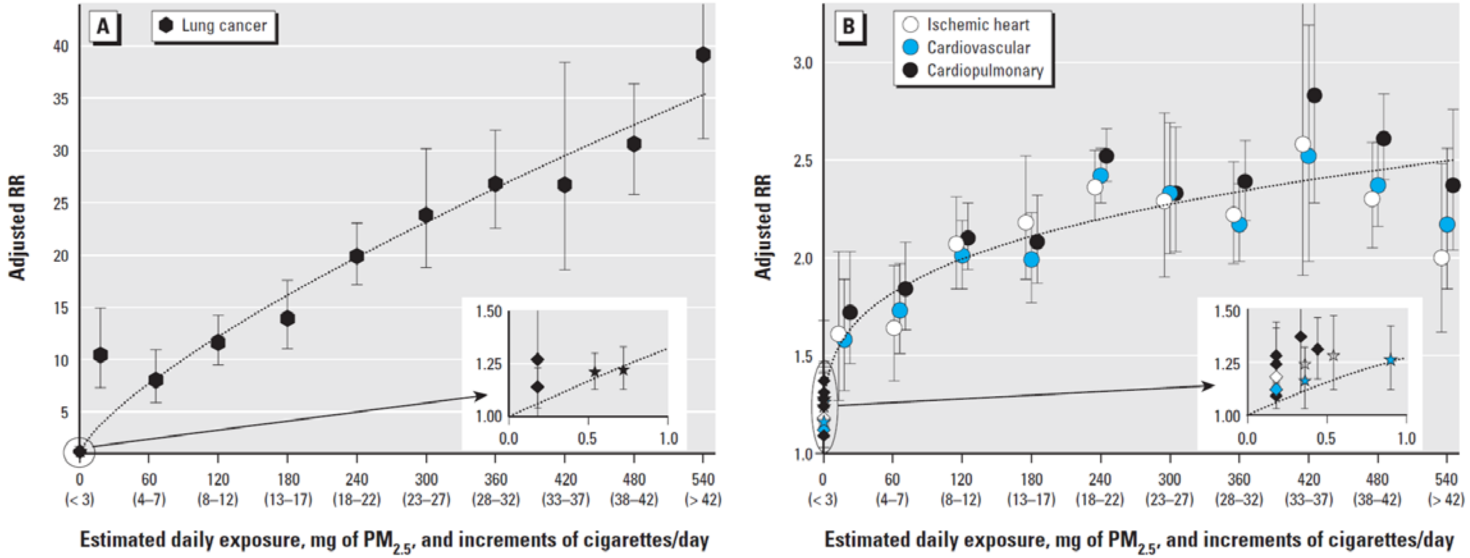
Quantitative exposure response studies and related meta-analyses

- Discussed extensively, critical comments resulted into multiple sensitivity analyses, additional exposure reconstruction and validation studies (HEI 2015; Crump 1999; 2001; Crump and Landingham 2012; Crump 2014; Crump et al. 2015; Moolgavkar et al. 2015; Morfeld and Spallek 2015, Mohner & Wendt, 2017, Vermeulen & Portengen, 2017, etc. etc.)

- Garshick et al., and Silverman et al., studies extensively reviewed by diesel epidemiology panel of the Health Effect Institute (2015)
    - General issues in the data analysis (adjustment for HWE by tenure)
    - Bias due to uncertainties in the reconstruction of historical exposure levels
    - Confounding by other risk factors; smoking, radon exposure
    - Co-exposure to other potential carcinogenic substances
- These two studies considered of sufficient quality for risk assessment, but uncertainties have to be taken into account

A few critical notes

- Epidemiology of diesel exhaust and lung cancer is generally narrowed to 3 (or 4) quantitative studies
- Job title studies are generally in line with the quantitative exposure response studies given known exposure levels and average duration of exposure
- Results in line with general air pollution epidemiology but quantitatively difficult to compare (Pope et al., EHP 2011)



A few critical notes

- Context of the Attfield/Silverman et al., study. Undertaken by US Governmental organizations. Highly protocolized, with the protocol based on what are considered best practices in occupational epidemiology and exposure estimation
- Re-analyses not protocolized but *post hoc* approaches
- How many sensitivity analyses will we conduct (At least one more under way)?

COI SCOEL Le Monde 25/2/2017

- Industry had a dramatic influence on the design, conduct, analysis of some of the studies and (re-)analysis in the US
- Non-reported conflicts of interest
- ‘Dieselgate’ in particular in Germany