*Int. J. Environ. Res. Public Health* **2014**, *11*, 1312-1340; doi:10.3390/ijerph110201312

OPEN ACCESS

International Journal of
**Environmental Research and Public Health**
**ISSN 1660-4601**
www.mdpi.com/journal/ijerph

*Review*

# Diesel Exhaust Exposure and the Risk of Lung Cancer—A Review of the Epidemiological Evidence

**Yi Sun *, Frank Bochmann †, Annette Nold † and Markus Mattenklott †**

Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA), Alte Heerstraße 111, Sankt Augustin 53773, Germany; E-Mails: frank.bochmann@dguv.de (F.B.); annette.nold@dguv.de (A.N.); markus.mattenklott@dguv.de (M.M.)

† These authors contributed equally to this work.

* Author to whom correspondence should be addressed; E-Mail: yi.sun@dguv.de;
Tel.: +49-2241-2312770; Fax: +49-2241-2312234.

*Received: 25 September 2013; in revised form: 5 December 2013 / Accepted: 12 December 2013 / Published: 27 January 2014*

---

**Abstract:** To critically evaluate the association between diesel exhaust (DE) exposure and the risk of lung cancer, we conducted a systematic review of published epidemiological evidences. To comprehensively identify original studies on the association between DE exposure and the risk of lung cancer, literature searches were performed in literature databases for the period between 1970 and 2013, including bibliographies and cross-referencing. In total, 42 cohort studies and 32 case-control studies were identified in which the association between DE exposures and lung cancer was examined. In general, previous studies suffer from a series of methodological limitations, including design, exposure assessment methods and statistical analysis used. A lack of objective exposure information appears to be the main problem in interpreting epidemiological evidence. To facilitate the interpretation and comparison of previous studies, a job-exposure matrix (JEM) of DE exposures was created based on around 4,000 historical industrial measurements. The values from the JEM were considered during interpretation and comparison of previous studies. Overall, neither cohort nor case-control studies indicate a clear exposure-response relationship between DE exposure and lung cancer. Epidemiological studies published to date do not allow a valid quantification of the association between DE and lung cancer.

**Keywords:** diesel exhaust; diesel motor emissions; DME; epidemiology; review; lung cancer

## 1. Introduction

Diesel engines have been widely used for decades in various industrial sectors such as underground mining, construction, public transportation, ship loading in docks, agriculture, operation of machines and fire-fighting. Diesel exhaust (DE) emissions are composed of gases and a particulate phase containing thousands of chemicals. Their composition varies according to engine type, speed, air/fuel ratio, temperature, fuel and many other factors [1]. DE contains large quantities of carbonaceous particulates to which polynuclear aromatic hydrocarbons and other heterocyclic compounds are adsorbed. The latter are known to be mutagenic and carcinogenic in both animals and humans [2].

In June 2012, a working group of the International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of DE in humans [3]. However, these findings appear to be based upon selected epidemiological studies with certain important methodological limitations, particularly in the assessment of confounding effects and the assessment of DE exposures [4]. In order to evaluate critically the epidemiological evidence for the association between DE exposure and the risk of lung cancer, we conducted a systematic review of the international literature.

## 2. Methods

### *2.1. Literature Search*

For comprehensive identification of original studies on the association between DE exposure and the incidence or mortality of lung cancer, searches were performed for the period between 1970 and 2013 in the following databases: MEDLINE, EMBASE, NIOSHTIC, CISDOC, Cochrane and the databases in TOXNET. Multipart search strategies were applied using “diesel” combined with the following search terms: “lung cancer”, “lung neoplasm?”, “work?”, “occupation?”, “epidemiol?”, “case control”, “cohort” or “risk”. Bibliographies and cross-referencing including comparison with reviews were additionally used for literature searches.

### *2.2. Quantification of DE Exposures Using MEGA-JEM*

Previous studies on the effect of DE exposure focus mainly on risk estimation for jobs supposed to involve high and prolonged exposure to DE, such as those of professional drivers, railroad workers, heavy equipment operators, and so on. Although a large number of studies have been published, few are able to provide any information on the level of DE exposures in these jobs.

To allow an objective impression to be gained of the level of DE exposures in commonly exposed jobs, we created a job-exposure matrix for DE exposures based upon historical industrial hygiene data from the MEGA (Measurement data relating to workplace exposure to hazardous substances) database (see Table 1).

**Table 1.** DE exposures in common exposed jobs in Germany (MEGA-JEM).

| **Job Titles** | **Exposure as Elemental Carbon (mg/m$^3$) (2)** | | |
|---|---|---|---|
| **(MEGA job title (1))** | **Before 1990 (3)** | **1990–1993 (4)** | **After 1993 (4)** |
| Dock workers,<br>Transportation equipment operators<br>(warehouse and loading work) | 0.19 | 0.05 | 0.03 |
| Heavy equipment operators<br>Drivers of heavy construction vehicles<br>(shipping and transport within enterprises) | 0.26 | 0.08 | 0.03 |
| Highway maintenance<br>Open-air mechanics<br>Highway workers<br>(repair and maintenance) | 0.13 | 0.04 | 0.02 |
| Mechanics (not open-air)<br>Bus garage workers<br>Truck mechanics<br>(bench tests) | 0.18 | 0.09 | 0.03 |
| Truck drivers<br>Heavy truck drivers<br>Professional drivers<br>Railroad workers<br>Bus drivers<br>Lorry drivers<br>Taxi drivers<br>(50% of exposure level of repair and maintenance) | 0.07 | 0.02 | 0.01 |
| Potash miner | 0.30 | 0.15 | 0.14 |

Notes: (1) Exposure data from MEGA are related to the listed job titles; (2) Exposure data are calculated from exposure data of total carbon (TC) using the known task related mean relation between EC and TC; (3) 90% percentile of the exposure data for the period 1990–1993; (4) 50% percentile of exposure data.

The MEGA database is a large industrial hygiene database forming part of the Measurement System for Exposure Assessment of the German Social Accident Insurance Institutions (MGU). The database was established in 1972 and contains more than 2.4 million historical measurements of around 1,380 industrial chemical and biological agents. In total, around 4,000 historical measurements of DE exposures were entered in the database for the period from 1990 to 2000.

In this review, MEGA-JEM was used directly to estimate the exposure levels of jobs given in the results of previous published studies. If information on exposure duration is available, cumulative doses of DE exposure were quantified as "exposure level (MEGA-JEM) × median exposure duration". Effect estimates published in previous studies were summarized in a scatter plot. Based on these values, exposure-response relationship between DE-exposure and lung cancer and their 95% CI were quantified by a linear regression analysis with the software package SigmaPlot 12.0. The inclusion of MEGA-JEM in this review will permit a direct comparison of previously published epidemiological evidence.

## 3. Results

In total, 42 cohort studies and 32 case-control studies were identified in which the association between DE exposure and lung cancer was examined.

### *3.1. Cohort Studies*

In general, historical industrial hygiene data on DE exposure (based on the measurement of elemental carbon) were not available in published cohort studies. Therefore, exposure assessment was limited only to job titles in 37 of the 42 identified cohort studies. Five studies allow a quantitative assessment of DE exposure based on industrial hygiene measurement. Three studies [5–7] quantified the DE exposures based upon historical surrogate measurements of nitrogen dioxide, while two other studies were based either on current industrial hygiene measurement of total carbon [8] or on historical surrogate measurements of CO [9].

The effect of DE exposure upon lung cancer was evaluated with the focus primarily on the following job categories: professional drivers, highway maintenance workers, railroad workers, mechanics, workers at gasoline filling stations, heavy equipment operators, dock workers and miners (see Table 2).

The effect of DE exposure was evaluated in most studies by comparison of the lung cancer risk among workers in highly exposed jobs with an external population by use of the standardized mortality ratio (SMR), standardized incidence ratio (SIR) or proportional mortality ratio (PMR). Internal comparison was carried out in nine cohort studies [2, 5–12]. All studies have large sample sizes. The possible confounding effect of smoking was adjusted in most of these studies (except the study by Bergdahl [7] and the study by Attfield [9]).

Boffetta *et al*. reported in an earlier study that railroad workers, heavy equipment operators, miners and truck drivers have higher mortality both for all causes and for lung cancer when compared with workers without exposure to DE [2]. Similar findings were also reported by Garshick *et al*. [11,13] and Larkin *et al*. [12]. However, a reanalysis of the US railroad study (originally published by Garshick [13]) indicates that the effect of DE exposure published in the early study appears to be unstable. The estimates of the effect vary strongly depending upon how the exposure was assessed and how confounders were considered in the analysis [14]. If the confounders were considered in a different manner, an exposure-response relationship between DE exposure and lung cancer is no longer observed. This early methodological disagreement in the US railroad study gives an example about how difficult previous evidence can be properly interpreted. This problem seems to be solved in a later published extended follow-up of this cohort [10]. Therefore, only the latest publication of this study [10] was considered in this review.

**Table 2.** Cohort studies on diesel exhaust exposure and lung cancer.

| Author | Population | Follow-up time period | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | RR/SMR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Ahlberg *et al*. (1981) [15] | 35,960 drivers and 686,708 non-drivers | 1961–1973 | Job as professional driver | Age, sex, local region | Mantel-Haenszel | Driver | 1.33 (1.13–1.56) | Impossible (exposure level and duration not available) |
| Attfield *et al*. (2012) [9] | 12,315 non-metal miners | 1947–1997 | Historical measurement of CO | Age, Work location | SMR Cox-model | Highest expo. (≥1,280 μg/m$^3$-year) | 2.39 (0.82–6.94) | Possible (unit: μg/m$^3$-year of respirable elemental carbon) |
| Balarajan *et al*. (1988) [16] | 3,392 professional drivers in London | 1950–1984 | Job as professional driver in 1939 | Age | SMR | Truck driver | 1.59 ($p < 0.05$) | Impossible (exposure level and duration not available) |
| | | | | | | Taxi driver | 0.86 ($p > 0.05$) | |
| | | | | | | Bus driver | 1.42 ($p > 0.05$) | |
| Bender *et al*. (1989) [17] | 4,849 highway maintenance workers | 1945–1984 | Job as highway maintenance worker | Age | SMR | Highway maintenance | 0,69 (0.52–0.90) | Impossible (exposure level and duration not available) |
| Bergdahl *et al*. (2010) [7] | 8,321 iron ore miners | 1958–2000 | 100,000 historical measurement of $NO_2$ | Age and calendar period | SIR, Poisson regression | >15 (ppm-year) | 0.87 (0.42–1.83) | Possible (unit: ppm-year of $NO_2$) |

**Table 2.** *Cont.*

| **Author** | **Population** | **Follow-up time period** | **Exposure assessment** | **Confounder controlled** | **Statistical method** | **Job title/exposure** | **RR/SMR (95% CI)** | **Quantification of exposure doses** |
|---|---|---|---|---|---|---|---|---|
| Boffetta *et al*. (1988) [2] | 461,981 males aged 40–79 years | 1982–1984 | Longest job with DME exposure | Age, smoking and other occupational exposures | Mantel-Haenszel | DE exposed | 1.18 (0.97–1.44) | Impossible (exposure level not available) |
| | | | | | | Truck driver | 1.24 (0.93–1.66) | |
| | | | | | | Railroad worker | 1.59 (0.94–2.69) | |
| | | | | | | Heavy equipment operator | 2.60 (1.12–6.06) | |
| Boffetta *et al*. (2001) [18] | All Swedish population employed without farmer | 1971–1989 | Job titles 1960–1970, DME yes/no | Age | SIR, Poisson regression | DE low | 0.95 (0.92–0.98) | Impossible (exposure level and duration not available) |
| | | | | | | DE medium | 1.1 (1.08–1.21) | |
| | | | | | | DE high | 1.3 (1.26–1.42) | |
| Garshick *et al*. (1988) [13] | 55,407 US railroad workers | 1959–1980 | Job title in 1959 DME yes/no | Age | Cox-model | DE exposure (1–4 years) | 1.20 (1.01–1.44) | Impossible (exposure level not available) |
| | | | | | | DE exposure (5–9 years) | 1.24 (1.06–1.44) | |
| | | | | | | DE exposure (10–14 years) | 1.32 (1.13–1.56) | |
| | | | | | | DE exposure (≥15 years) | 1.82 (1.30–2.55) | |
| Garshick *et al*. (2004) [19] | 54,973 US railroad workers | 1959–1996 | Job title in 1959 DME yes/no | Age, year of employment | Cox-model | DE exposed | 1.40 (1.30–1.51) | Impossible (exposure level not available) |

**Table 2.** *Cont.*

| Author | Population | Follow-up time period | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | RR/SMR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Garshick *et al.* (2006) [10] | 39,388 US railroad workers | 1959–1996 | Job title in 1959 DME yes/no | Age, Smoking | Cox-model | DE exposed | 1.22 (1.12–1.32) | Impossible (exposure level not available) |
| | | | | | | Conductor (<5 years) | 1.31 (1.12–1.51) | |
| | | | | | | Conductor (5–10 years) | 1.23 (1.08–1.39) | |
| | | | | | | Conductor (10–15 years) | 1.23 (1.08–1.39) | |
| | | | | | | Conductor (15–20 years) | 1.16 (1.03–1.30) | |
| | | | | | | Conductor (≥20 years) | 1.22 (1.02–1.47) | |
| Garshick *et al.* (2008) [11] | 31,135 truck industry workers | 1985–2000 | Job title (ever employed ≥ 1 year) | Age, race, smoking, healthy worker effect | Cox-model | Long-haul driver (20 years) | 1.40 (0.88–2.24) | Impossible (exposure level not available) |
| | | | | | | Pickup driver (20 years) | 2.21 (1.38–3.52) | |
| | | | | | | Dockworker (20 years) | 2.02 (1.23–3.33) | |
| | | | | | | Combination (20 years) | 2.34 (1.42–3.83) | |
| Guberan *et al.* (1992) [20] | 6,630 professional drivers | 1949–1986 | Job documen-ted as profess-ional driver | Age | SMR (SIR) | Driver | 1.50 (1.23–1.81) | Impossible (exposure level and duration not available) |

**Table 2.** *Cont.*

| Author | Population | Follow-up time period | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | RR/SMR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Guo *et al.* (2004) [6] | All economically active Finns on 31 December 1970 (*n* = 1,180,231) | 1971–1995 | Work history documented in Population Census File, FIN-JEM (historical measurement of $NO_2$) | Smoking, asbestos, silica and socio-economic status | Poisson regression | DE low (0.1–1.9)<br>DE middle (2.0–9.9)<br>DE high (≥10) | 0.98 (0.94–1.03)<br>1.04 (0.94–1.03)<br>0.95 (0.94–1.03) | Possible (unit: $mg/m^3$-year) |
| Gustafsson *et al.* (1986) [21] | 6,071 Swedish dock workers | 1961–1980 | Job as dock worker | Age | SMR (SIR) | Dock worker | 1.29 (1.02–1.63) | Impossible (exposure level and duration not available) |
| Haldorsen *et al.* (2004) [22] | All Norwegians in 1970, age: 25–64 | 1971–1991 | Job title | Age, smoking | SIR | Driver<br>Engine/motor operator workers | 1.58 (1.5–1.7)<br>1.34 (1.2–1.5) | Impossible (exposure level and duration not available) |
| Hansen (1993) [23] | 14,225 truck drivers | 1970–1980 | Self-reported job as truck driver in 1970 | Age | SMR | Truck driver | 1.6 (1.28–1.98) | Impossible (exposure level and duration not available) |
| Howe *et al.* (1983) [24] | 43,826 retired railway workers | 1965–1977 | Job at time of retirement, DME yes/no | Age | SMR | DE probably exposed | 1.35 ($p < 0.001$) | Impossible (exposure level and duration not available) |
| Jakobsson *et al.* (1997) [25] | 96,438 professional drivers in Sweden | 1971–1984 | Job in 1970 | Age, smoking (indirect adjustment) | SMR | Taxi driver<br>Long-distance lorry driver<br>Short-distance lorry driver | 1.2 (1.0–1.4)<br>1.1 (0.9–1.3)<br>1.2 (1.0–1.7) | Impossible (exposure level and duration not available) |

**Table 2.** *Cont.*

| Author | Population | Follow-up time period | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | RR/SMR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Järvholm *et al*. (2003) [26] | 20,728 drivers and 119,984 carpenters/ electricians | 1971–1995 | Job documented in health examination | Age | SMR (SIR) | Equipment operator<br>Truck driver | 0.76 (0.58–0.97)<br>1.14 (0.87–1.46) | Impossible (exposure level and duration not available) |
| Johnston *et al*. (1997) [5] | 18,166 British coalminers | 1969–1992 | historical measurement of NO, $NO_2$ | Age, smoking | Cox-model | Risk/unit exposure | 1.23 (1.0–1.5) | Possible (unit: $g/m^3$-hour) |
| Kaplan (1959) [27] | 6,506 deceased railroad workers in US | 1953–1958 | Job documented in medical record | Age | SMR | Railroad worker | 0.88 (0.65–1.16) | Impossible (exposure level and duration not available) |
| Laden *et al*. (2007) [28] | 54,319 male employees in US | 1985–2000 | Job title | Age | SMR | Driver<br>Dockworker | 1.1 (1.02–1.19)<br>1.1 (0.94–1.30) | Impossible (exposure level and duration not available) |
| Lagorio *et al*. (1992) [29] | 1,446 workers of gasoline filling station | 1981–1991 | Employment duration | Age | SMR | Filling station worker | 1.06 (0.64–1.65) | Impossible (exposure level not available) |
| Larkin *et al*. (2000) [12] | 55,395 US railroad workers | 1959–1976 | Job title in 1959 DME yes/no | Age, smoking | Poisson regression | Engineer/fireman<br>Brakemen/ conductor<br>Shop worker | 1.17 (0.79–1.74)<br>1.08 (0.76–1.54)<br>1.21 (0.80–1.83) | Impossible (exposure level not available) |
| Luepker *et al*. (1978) [30] | 184,435 truck drivers | 3 months in 1976 | Union membership | Age | SMR | Truck driver | 1.21 ($p > 0.05$) | Impossible (exposure level and duration not available) |

**Table 2.** *Cont.*

| Author | Population | Follow-up time period | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | RR/SMR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Magnani *et al*. (1988) [31] | All population in England and Wales | 1971–1971 | Decennial JEM for death cases, estimation of risk set | Age<br>social class | SMR | DE low<br>DE middle<br>DE high | 0.98<br>0.95<br>0.96 | Impossible (exposure level and duration not available) |
| Maizlish *et al*. (1988) [32] | 1,570 deceased highway workers | 1970–1983 | CalTRANS employees | Age | PMR | Highway worker | 0.98 (0.80–1.19) | Impossible (exposure level and duration not available) |
| Menck and Henderson (1976) [33] | Estimated population at risk in 1971 in Los Angeles | 1968–1973 | Job documented in death certificates | Age | SMR | Taxi driver<br>Truck driver<br>Auto repair<br>Transportation | 3.44<br>1.65<br>1.46<br>1.27 | Impossible (exposure level and duration not available) |
| Milham (1983) [34] | 429,926 male and 25,066 female deaths | 1950–1979 | Job during most of lifetime | Age | PMR | Railroad worker<br>Machine operator | 1.2<br>1.4 | Impossible (exposure level and duration not available) |
| Netterstrom (1988) [35] | 2,465 bus drivers | 1978–1984 | Job in 1978 | Age | SMR | Bus driver | 0.55 (0.33–0.99) | Impossible (exposure level and duration not available) |
| Neumeyer-Gromen *et al*. (2009) [8]<br>Säverin *et al*. (1999) [36] | 5,862 potash miners | 1970–2001 | 255 measurement of TC value in 1992 | Age, smoking | SMR<br>Poisson regression, Cox-model | DE exposure (<1.29)<br>DE exposure (1.26–2.04)<br>DE exposure (2.04–2.73)<br>DE exposure (2.73–3.90)<br>DE exposure (>3.90) | 1.0<br>1.13 (0.46–2.75)<br>2.47 (1.02–6.02)<br>1.50 (0.56–4.04)<br>2.28 (0.87–5.97) | Yes (unit: $mg/m^3$-year) |

**Table 2.** *Cont.*

| Author | Population | Follow-up time period | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | RR/SMR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Nokso-Koivisto and Pukkala (1994) [37] | 8,391 locomotive drivers | 1953–1991 | Member of association | Age | SIR | Locomotive driver | 0.86 (0.75–0.97) | Impossible (exposure level and duration not available) |
| Paradis *et al*. (1989) [38] | 2,134 bus drivers | 1962–1985 | Job in payroll | Age | SMR | Bus driver | 1.01 (0.70–1.38) | Impossible (exposure level and duration not available) |
| Pukkala *et al*. (1983) [39] | All population in Finland, (age: 35–69) | 1971–1975 | Job in 1970 | Age | SIR | Railway driver<br>Road transport | 0.58 ($p > 0.05$)<br>1.06 ($p > 0.05$) | Impossible (exposure level and duration not available) |
| Raffle (1957) [40] | London transport male staff | 1950–1953 | Job in 1950 | Age | SMR | Bus driver | 1,4 (0.94–2.0) | Impossible (exposure level and duration not available) |
| Raffnson (1988) [41] | 295 marine engineers und 182 machinists | 1955–1982 | Job documented in the Register of Engineers | Age | SMR | Marine engineer | 2.05 (0.83–4.23) | Impossible (exposure level and duration not available) |
| Rafnsson and Gunnarsdottir (1991) [42] | 888 truck drivers and 726 taxi drivers alive in 1951 | 1951–1988 | Job documented in truck driver union | Age | SMR | Truck driver<br>Taxi driver | 2.14 (1.37–3.18)<br>1.39 (0.72–2.43) | Impossible (exposure level and duration not available) |
| Rushton *et al*. (1983) [43] | 8,490 transport maintenance workers | 1967–1975 | Last or present job documented | Age | SMR | Maintenance Worker | 1.01 (0.82–1.22) | Impossible (exposure level and duration not available) |
| Schenker (1984) [44] | 2,519 railroad workers | 1967–1979 | Job title in retirement board, DME: Yes/No | Age | SMR | DE exposed | 1.42 (0.92–1.92) | Impossible (exposure level and duration not available) |

**Table 2.** *Cont.*

| Author | Population | Follow-up time period | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | RR/SMR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Stern *et al*. (1981) [45] | 1,558 motor vehicle examiners | 1944–1977 | Ever employed job | Age | SMR | Motor vehicle examiner | 1.02 (0.6–2.0) | Impossible (exposure level and duration not available) |
| Stern *et al*. (1997) [46] | Death of 15,843 construction operating engineers | 1988–1993 | Job title | Age | PMR | construction operating engineers | 1.14 (1.09–1.19) | Impossible (exposure level and duration not available) |
| Waller (1981) [47] | Transport workers in London 420,699 man-years at risk | 1950–1974 | Job in 1950 | Age | SMR | Bus driver | 0.79 (0.73–0.85) | Impossible (exposure level and duration not available) |
| Waxweiler (1973) [48] | 4,944 potash miners, US | 1940–1967 | Ever employed in a potash firm | Age | SMR | Potash miner | 1.1 (0.69–1.66) | Impossible (exposure level and duration not available) |
| Wong *et al*. (1985) [49] | 34,156 construction workers in US | 1964–1978 | Heavy equipment operators ≥20 year, duration of union membership | Age | SMR | Union membership | 1,07 (1.00–1.15) | Impossible (exposure level not available) |

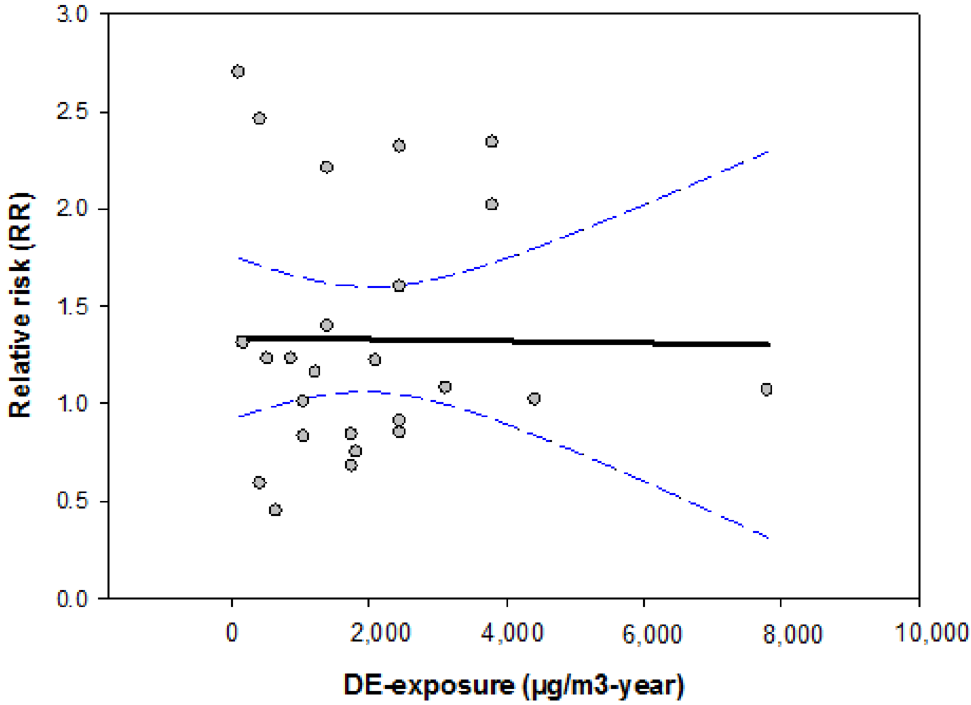
Among the three cohort studies employing historical measurements of nitro compounds as surrogate indicators of DE exposures [5–7], a weak association (OR = 1.23, 95% CI: 1.0–1.5) between DE exposure and lung cancer can be demonstrated only in the study by Johnston *et al*. [5]. In the other two cohort studies [6–7], no relationship between DE exposure and lung cancer could be observed. Main strengths of these studies are large sample size, quantitative exposure estimations and consideration of smoking as a confounder in the analysis. However, some important limitations make the interpretation of these studies difficult. These include the population based setting and incomplete assessment of work history in the study by Guo *et al*. [6], and the missing consideration of occupational cofounders (such as respirable silica) in the analysis of the other two mining cohorts [5,7]. Since it is generally questionable if nitro compounds can be used as surrogate to measure DE exposures, the evidences provided by these studies are rather limited.

The German potash miner study [8] is the first study which quantified DE exposures by measuring carbon compounds. This study has a sample size of 5,862 workers with a follow-up duration of 30 years. After adjustment for age and smoking, the study demonstrates a clear exposure-response relationship between DE exposures and lung cancer mortality. However, in a recent reanalysis of this study, Möhner *et al*. [50] pointed out that a part of cohort members in this study were previously employed as uranium miners. These workers may have had a high exposure to respirable silica and radon daughters in their work history. If these subjects were excluded from the data analysis, an exposure-response relationship between DE exposure and lung cancer can no longer be observed. This finding leads to a further reanalysis of this cohort in which employment in external mines or industries was controlled [51]. The final results give no evidence of an association between DE exposure and lung cancer. Strengths of this study are large sample size and extensive control of both occupational and non-occupational confounders in the analysis [50, 51]. Historical DE exposures were estimated based on the current industrial hygiene measurements.

In contrast to the German potash miner study, the US Miners study demonstrates an extremely high effect of DE exposure (up to 5-fold), although the initial analysis of this cohort did not reveal a clear relationship between DE exposure and lung cancer [9]. Main strengths of this study are large sample size (more than 12,000 workers with an average follow-up duration of about 23 years), quantitative assessment of DE exposures by measuring carbon compounds and the adjustment of smoking as a confounder in a nested case-control analysis [52]. However, some findings reported in this study need more clarification. For example, it is unclear why “surface only workers” (SMR = 1.33) have the same risk as the “ever underground workers” (SMR = 1.21) in the initial analysis, although DE exposure among “underground workers” was about 500 times higher than “surface workers”. This finding seems to be contradictory with the final reported high effect of DE exposures. Possible limitations of this study have been discussed by Morfeld [53] and Gamble *et al*. [54] regarding the completeness of follow-up, essential exposure misclassification, inadequate control of occupational confounder and improper statistical methods used.

In order to compare previously published cohort studies objectively and to allow an overall judgement of the association between DE exposure and lung cancer, we calculated the historical DE exposure in previous studies by means of the MEGA-JEM. Due to limited exposure information (limited information on job title or exposure duration), cumulative doses of DE exposures are only available for six cohort studies (Table S1, Supplementary Information). The results of these studies are summarized in Figure 1. Overall, no exposure-response relationship between DE exposure and lung cancer can be demonstrated.

**Figure 1.** Effects of DE-exposures on the risk of lung cancer given in previously published cohort studies.




### *3.2. Case-Control Studies*

In total, 25 population or hospital-based case-control studies, six nested case-control studies and 1 industry-based case-referent study were identified (see Table 3). Most of these studies have large sample sizes and adjustment of the possible confounding effect of smoking in the analysis.

Assessments of DE exposures were limited in most of these studies on job title (with different definitions) or dichotomous categorization (ever/never exposed). Quantitative or semi-quantitative assessment of DE exposure was carried out in only six studies, with use of different exposure assessment methods [51,52,55–58]. Overall, a consistently increased risk of lung cancer was reported for jobs supposed to have high DE exposures. An exposure-response relationship was also presented in most studies. However, due to the different exposure assessment methods used, direct comparison between these studies is difficult.

**Table 3.** Case-control studies on diesel exhaust exposure and lung cancer.

| Author | Design | Population | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | OR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Benhamou *et al.* (1988) [59] | Population based case-control study | 1,625 cases and 3,091 controls | Ever employed as professional driver | Age, smoking | Conditional logistic regression | Motor vehicle driver<br>Transport equipment operator<br>Miner<br>Farmers | 1.42 (1.07–1.89)<br>1.35 (1.05–1.75)<br>2.14 (1.07–4.31)<br>1.24 (0.94–1.62) | Impossible (exposure level and duration not available) |
| Boffetta *et al.* (1990) [60] | Population based case-control study | 2,584 cases and 5,099 controls | Self reported exposure (yes/no) | Age, race, smoking, education and asbestos | Logistic regression | Probable DE exposure (≥30 years)<br>Truck driver (1–15 years)<br>Truck driver (16–30 years)<br>Truck driver (>30 years) | 1,49 (0,72–3,11)<br>1,83 (0,31–10,73)<br>0,94 (0,41–2,15)<br>1,17 (0,40–3,41) | Impossible (exposure level not available) |
| Brüske-Hohlfeld *et al.* (1999) [61] | Population based case-control study | 3,498 cases and 3,541 controls | Interview on work history | Age, smoking and Asbestos | Conditional logistic regression | DE exposed | 1,43 (1,23–1,67) | Impossible (exposure level and duration not available) |
| Buiatti *et al.* (1985) [62] | Population based case-control study | 376 cases and 892 controls | Ever employed job transportation | Age and smoking | Logistic regression | Transportation<br>Taxi driving<br>Train conductor | 1.1 (0.7–1.6)<br>1.8 (1.0–3.4)<br>1.4 (0.5–3.9) | Impossible (exposure level and duration not available) |

**Table 3.** *Cont.*

| Author | Design | Population | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | OR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Burns (1991) [63] | Population based case-control study | 5,935 cases and 3,956 controls with colon cancer | Telephone interview on work history, job title | Age and smoking | Logistic regression | Automobile repair<br>Railroad<br>Bus and truck transport | 1.56 (0.85–2.87)<br>1.37 (0.70–2.66)<br>1.20 (0.82–1.75) | Impossible (exposure level and duration not available) |
| Coggon *et al.* (1984) [64] | Population based case-control study | 598 cases and 1,180 controls | Job in death certificate DME (yes/no) | Age, sex and residence | Logistic regression | High DE jobs | 1.1 (0.7–1.8) | Impossible (exposure level and duration not available) |
| Damber and Larsson (1987) [65] | Population based case-control study | 589 cases and 1,035 controls | Self reported work history | Age and smoking | Logistic regression | Professional driver (>1 years)<br>Professional driver (>10 years)<br>Professional driver (>20 years) | 1.36 (0.97–1.91)<br>1.47 (0.97–2.20)<br>1.61 (1.01–2.57) | Impossible (exposure level not available) |
| Decoufle *et al.* (1977) [66] | Hospital based case-control study | Cases and controls were selected among 13,949 patients | Job title | Age and smoking | unclear | Bus driver<br>Taxi driver<br>Truck driver | 1.81 ($p < 0.05$)<br>0.82 ($p < 0.05$)<br>1.07 ($p < 0.05$) | Impossible (exposure level and duration not available) |
| Elci *et al.* (2003) [67] | Hospital based case-control study | 1,354 cases and 1,519 controls | Job title | Age and smoking | Logistic regression | Driver<br>Highway construction | 1.4 (1.1–2.0)<br>1.5 (1.1–2.5) | Impossible (exposure level and duration not available) |

**Table 3.** *Cont.*

| Author | Design | Population | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | OR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Emmelin (1993) [55] | Industry based case-referent study | 50 cases and 154 controls (dock workers) | Job as dock worker. Index for DME exposure | Age and smoking | Conditional logistic regression | Low DE | reference | Impossible (exposure level and duration not available) |
| | | | | | | Medium DE | 1.6 (0.5–5.1) | |
| | | | | | | High DE | 2.9 (0.8–10.7) | |
| Garshick *et al.* (1987) [68] | Nested case-control study | Deceased railroad workers. 1,256 cases and 2,385 controls | Expert evaluation for jobs, exposure duration | Age, smoking and asbestos | Logistic regression | Railroad (>20 years) | 1.55 (1.09–2.21) | Impossible (exposure level not available) |
| | | | | | | DE exposed (>20 years) | 1.41 (1.06–1.88) | |
| Gustavsson *et al.* (1990) [56] | Nested case-control study | 20 cases and 120 controls | Index for exposure level, exposure duration | Age and asbestos | Conditional logistic regression | Index value 1 (0–10) | Reference | Impossible (exposure level and duration not available) |
| | | | | | | Index value 2 (10–20) | 1.34 (1.09–1.64) | |
| | | | | | | Index value 3 (20–30) | 1.81 (1.20–2.71) | |
| | | | | | | Index value 4 (>30) | 2.43 (1.32–4.47) | |
| Gustavsson *et al.* (2000) [57] | Population based case-referent study | 1,042 cases and 1,274 controls | historical measurement of $NO_2$ | Age, smoking, radon | Logistic regression | 0–0.53 | 0.67 (0.42–1.08) | DME was calculated as cumulative $NO_2$ exposure (mg/m$^3$-year) |
| | | | | | | 0.54–1.41 | 1.14 (0.77–1.67) | |
| | | | | | | 1.42–2.37 | 1.01 (0.67–1.53) | |
| | | | | | | ≥2.38 | 1.62 (1.13–2.31) | |

**Table 3.** *Cont.*

| Author | Design | Population | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | OR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Hall *et al*. (1984) [69] | Hospital based case-control study | 502 cases and 502 controls | Interview on job title | Age, smoking and social status | Mantel-Haenszel | Bus driver | 5.5 (0.8–36.0) | Impossible (exposure level and duration not available) |
| | | | | | | Truck driver | 1.4 (0.7–2.6) | |
| | | | | | | Railroad worker | 2.6 (0.5–12.8) | |
| | | | | | | Heavy equipment | 3.5 (1.0–11.8) | |
| Hansen *et al*. (1998) [70] | Population based case-control study | 37,597 cases and 37,597 controls | Job title documented in National Bureau of Statistics | Age and sex | Conditional logistic regression | Taxi driver | 1.6 (1.2–2.2) | Impossible (exposure level and duration are not available) |
| | | | | | | Bus and truck driver | 1.3 (1.2–1.5) | |
| Hayes *et al*. (1989) [71] | Population based case-control study | 1,444 cases and 1,893 controls | Interview, motor exhaust-related jobs, employment duration | Age, smoking and study area | Logistic regression | Truck driver (≥10 years) | 1.5 (1.1–1.9) | Impossible (exposure level not available) |
| | | | | | | Bus driver (≥10 years) | 1.6 (0.9–2.8) | |
| | | | | | | Mechanics (≥10 years) | 1.7 (0.9–3.4) | |
| | | | | | | Heavy equipment (≥10 years) | 1.3 (0.6–3.1) | |

**Table 3.** *Cont.*

| Author | Design | Population | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | OR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Kauppinen (1993) [72] | Nested case-control study | 136 cases and 408 controls | JEM for job title, DME (yes/no) | Age, smoking | Conditional logistic regression | DE exposed | 1.70 (0.55–5.20) | Impossible (exposure level and duration not available) |
| Lerchen *et al*. (1987) [73] | Population based case-control study | 506 cases and 771 controls | High risk jobs ever exposed? | Age, sex, race and smoking | Logistic regression | Engineer and fireman<br>Diesel engine mechanic<br>ME exposure | 0.6 (0.1–3.3)<br>0.6 (0.2–2.0)<br>0.6 (0.2–1.6) | Impossible (exposure level and duration not available) |
| Milne *et al*. (1983) [74] | Population based case-control study | 925 cases and 6,420 cancer controls | Job title in death certificates | Age and sex | Logistic regression | Transportation | 1.1 | Impossible (exposure level and duration not available) |
| Möhner *et al*. (2013) [51] | Nested case-control study | 68 cases and 340 controls | 255 measurement of TC value in 1992 | Age, smoking, external employment | Conditional logistic regression | 1st quartile<br>2nd quartile<br>3rd quartile<br>4th quartile | reference<br>0.90<br>1.16<br>0.78 | Yes (unit: μg/m$^3$-year) |
| Olsson *et al*. (2011) [75] | Pooled analysis of 11 case-control studies | 13,304 population cases and 16,282 controls | | | Logistic regression | Exposure index > 34.5 | 1.31 (1.19–1.43) | Impossible (exposure level not available) |
| Parent *et al*. (2007) [76] | Population based case-control study | 857 cases and 1,882 controls | | | Logistic regression | DE exposure | 1.2 (0.8–1.8) | Impossible (exposure level not available) |
| Pfluger and Minder (1994) [77] | Population based case-control study | Deceased chauffeurs | Job title in death certificates | Age and smoking | Poisson regression | Chauffeur | 1.48 (1.30–1.68) | Impossible (exposure level and duration not available) |

**Table 3.** *Cont.*

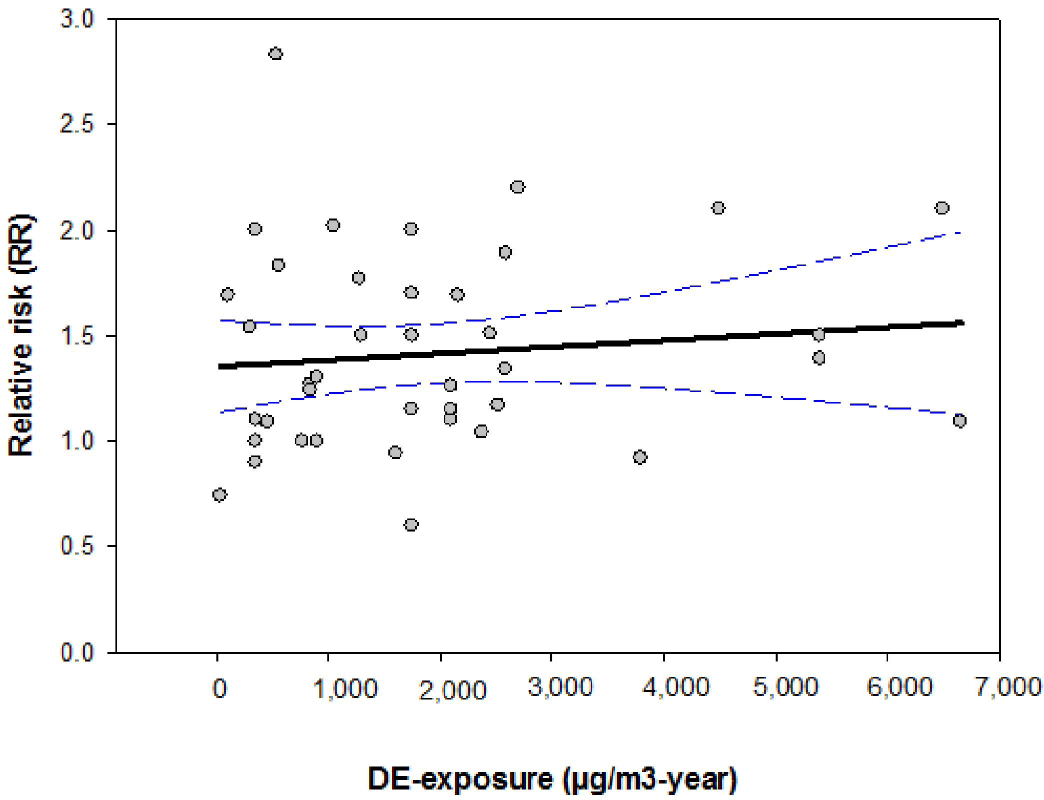
| Author | Design | Population | Exposure assessment | Confounder controlled | Statistical method | Job title/exposure | OR (95% CI) | Quantification of exposure doses |
|---|---|---|---|---|---|---|---|---|
| Richiardi *et al*. (2006) [78] | Population based case-control study | 595 cases and 845 controls | Job title, DME (yes/no) | Age, sex, smoking and other occupational exposures | Logistic regression | DE exposure | 1.04 (0.79–1.37) | Impossible (exposure level and duration not available) |
| Siemiatycki *et al*. (1988) [79] | Hospital based case-control study | 857 cases and 1,523 controls | Interview on work history, expert judgement on DE exposure | Age, race, social status, smoking and blue/white collar job | Mantel-Haenszel | DE exposed | 1.2 (0.8–1.5) | Impossible (exposure level and duration not available) |
| Silverman *et al*. (2012) [52] | Nested case-control study | 198 cases and 562 controls from 8 mining companies | 1,156 measurement of EC value during 1998–2001 | Age, sex, race, smokig and history of respiratory disease | Conditional logistic regression | DE exposure (0–19) | Reference | Yes (unit: $\mu g/m^3$-year) |
| | | | | | | DE exposure (19–246) | 0.87 (0.48–1.59) | |
| | | | | | | DE exposure (246–964) | 1.50 (0.67–3.36) | |
| | | | | | | DE exposure (≥964) | 1.75 (0.77–3.97) | |
| Soll-Johanning *et al*. (2003) [80] | Nested case-control study | 153 cases and 606 controls | Job as bus driver | Age and smoking | Conditional logistic regression | 20+ years of employment | 0.63 (0.32–1.14) | Impossible (exposure level not available) |
| Steenland *et al*. (1990) [81] | Population based case-control study | 996 cases and 1,085 controls | Interview next of kin, longest job as truck driver | Age, smoking and asbestos | Multivariate analysis | Truck driver (≥18 year) | 1.55 (0.97–2.47) | Impossible (exposure level not available) |
| | | | | | | Truck mechanic (≥18 year) | 1.50 (0.59–3.40) | |

**Table 3.** *Cont.*

| **Author** | **Design** | **Population** | **Exposure assessment** | **Confounder controlled** | **Statistical method** | **Job title/exposure** | **OR (95% CI)** | **Quantification of exposure doses** |
|---|---|---|---|---|---|---|---|---|
| Swanson *et al*. (1993) [82] | Population based case-control study | 3,797 cases and 1,966 controls (colon cancer) | Interview relatives, last job title, employment duration | Age, race and smoking | Logistic regression | Industrial maintenance (20+ years) | 1.5 (0.8–2.9) | Impossible (exposure level not available) |
| | | | | | | Automobile mechanics (20+ years) | 1.5 (0.7–3.0) | |
| | | | | | | Machine operators (20+ years) | 1.9 (1.0–3.9) | |
| | | | | | | Heavy truck driver (20+ years) | 2.5 (1.4–4.4) | |
| | | | | | | Light truck driver (20+ years) | 2.1 (0.9–4.6) | |
| Villeneuve *et al*. (2011) [58] | Population based case-control study | 1,681 cases and 2,053 controls | Expert evaluation for jobs | Age, smoking, location, silica and asbestos | Logistic regression | Cumul. expo. 1. tertile | 0.93 (0.75–1.17) | Impossible (exposure level and duration not available) |
| | | | | | | Cumul. expo. 2. tertile | 1.03 (0.83–1.29) | |
| | | | | | | Cumul. expo. 3. tertile | 1.12 (0.89–1.40) | |
| Wegman and Peters (1978) [83] | Population based case-control study | 100 cases and 100 controls of CNS cancer | Tele. Interview relatives on job title | No | Logistic regression | Transportation equipment operator | 1.26 (0.28–5.84) | Impossible (exposure level and duration not available) |

To facilitate the comparison of previously published case-control studies, we assessed the DE exposure quantitatively by means of the MEGA-JEM. Due to limited exposure information, cumulative doses of DE-exposures can only be quantified for eight case-control studies (Table S2, Supplementary Information). The results of these studies are summarized in Figure 2. Similar to previously published cohort studies, case-control studies do not show a clear exposure-response-relationship.

**Figure 2.** Effects of DE-exposures on the risk of lung cancer given in previously published case-control studies.




## 4. Discussion

The possible association between DE and lung cancer, which constitutes an important occupational health question, has long been the subject of debate. Interpretation of epidemiological evidence faces a series of methodological challenges.

Lack of exposure information appears to be the major problem in interpreting human epidemiological data. The low volume of data documenting past exposures is due to the fact that no standardized method of measuring diesel fumes existed before the late 1980s. From an industrial hygiene prospective, it was not clear which substance to measure during assessment of occupational exposure to DE. Diesel fumes are composed of gases (nitrogen oxides, carbon monoxide) and various hydrocarbons bound to a carbon core. Early studies have reported levels of particulate, but such particulates are generated by many sources other than diesel engines [84]. Attention has also been focused on polycyclic aromatic hydrocarbons (PAHs) and nitro-PAHs in the exhaust. However, there are no standard methods of measuring PAHs, and PAHs are also emitted by sources other than diesel engines [84].

In the late 1980s, a standardized method of measuring diesel fumes by quantifying elemental carbon was introduced. Since then, systematic industrial hygiene measurements have been begun in some industrialized countries. However, a long time is needed for sufficient measurement data to be collected for use in epidemiological research. Most of the epidemiological studies published to date therefore provide no fundamental basis for an objective assessment of DE exposures.

In this review, we identified only two recent studies containing industrial hygiene measurement data for carbon compounds. In all remaining studies, the exposure assessments are based on expert judgements. A given job may be classified as having high exposure by one expert, but low by another [14,85]. Previous studies indicate that the differences in expert opinion have a strong influence on the estimated exposure-response relationship between DE exposure and lung cancer [14,85]. This problem makes the interpretation and comparison of previously published epidemiological studies difficult.

To facilitate an objective comparison of previously published epidemiological studies, we created a JEM for DE exposures based upon a large number of standardized industrial hygiene measurements conducted since the late 1980s. Three calendar periods were considered in the JEM, since most of the technical changes occurred during the period between 1990 and 1993. The values in the MEGA-JEM were considered in the interpretation of the epidemiological studies published to date. We found that conflicting findings were reported not only between studies, but also within studies. It is very common for jobs associated with higher exposure (according to the exposure value given in Table 1) to be reported as having lower risks than jobs with lower exposure, even within the same study. Since many studies indicated only job titles without detailed information on the exposure duration, direct comparison of the effect estimates was limited. To solve this problem, we summarized only studies with complete exposure information (both job title and exposure duration) and presented the results in Figures 1 and 2. Overall, neither cohort nor case-control-studies show exposure-response relationship between DE exposure and lung cancer.

Caution should be exercised during interpretation of these studies. Previous cohort studies often compare workers in certain job categories with a standard population without adjustment for important confounders, while case-control studies generally employ a population-based design which is less suitable for detecting weak associations related to DE exposures. For some of the early epidemiological studies, latency may also be too short to attribute lung cancer to DE exposure. The use of different definitions of job titles in the analysis (longest job, ever employed jobs, census job, job in death certificates or at the time of medical examination, *etc*.) and the related cross-contamination with current and previous occupational history may also have a strong influence on the estimated effects. This problem was clearly demonstrated in the cohort of German potash miners, for which the study results were strongly dependent upon whether previous work history in the uranium mining industry was considered in the analysis [50]. The JEM-approach used in this review has also some weaknesses. First, the exposure duration in most studies is given only in categories. Therefore, the use of the center of such category gave only a very crude estimate for the mean or the median of exposure duration. Furthermore, the JEM used in this review is based on German industrial hygiene measurement data. The data collected in Germany may not be representative for all industrialized countries. Since diesel engines were introduced into the workplace at variable rates over time by industry and country, the use of MEGA-JEM in this review may lead to some uncertainty in the exposure assessment. However, despite the exposure-assessment methods used (expert judgement, measuring nitro compounds, measuring carbon compound, MEGA-JEM) no consistent findings of an association between DE exposures and lung cancer can be demonstrated.

## 5. Conclusions

Overall, the previously published epidemiological evidence did not clearly support an exposure-response relationship between DE exposure and lung cancer. In fact, the limited exposure information available in previous studies does not even allow a valid estimation of an association between DE exposure and lung cancer. However, such an association cannot be ruled out. Causality of weak association is often difficult to establish, since it is susceptible to all forms of possible design bias. Due to the limited epidemiological evidence to date, well designed studies in an industrial context are still needed, for which detailed exposure assessment methods and adequate control for confounders are recommended.

## Author Contributions

All authors participate in drafting the article or revising it critically for important intellectual content; and give final approval of the version to be submitted and revised.

## Conflicts of Interest

The authors declare no conflict of interest.

## References

1. Schuetzle, D.; Frazier, J.A. Factors influencing the emission of vapor and particulate phase components from diesel engines. *Dev. Toxicol. Environ. Sci.* **1986**, *13*, 41–63.
2. Boffetta, P.; Stellman, S.D.; Garfinkel, L. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. *Amer. J. Ind. Med.* **1988**, *14*, 403–415.
3. Benbrahim-Tallaa, L.; Baan, R.A.; Grosse, Y.; Lauby-Secretan, B.; El Ghissassi, F.; Bouvard, V.; Guha, N.; Loomis, D.; Straif, K. International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. *Lancet Oncol.* **2012**, *13*, 663–664.
4. Pallapies, D.; Taeger, D.; Bochmann, F.; Morfeld, P. Comment: Carcinogenicity of diesel-engine exhaust (DE). *Arch. Toxicol.* **2013**, *87*, 547–549.
5. Johnston, A.M.; Buchanan, D.; Robertson, A.; Miller, B.G. Investigation of the Possible Association between Exposure to Diesel Exhaust Particulates in British Coalminers and Lung Cancer; IOM Research Report TM/97/08: Edingburg, UK, 1997.
6. Guo, J.; Kauppinen, T.; Kyyrönen, P.; Lindbohm, M.L.; Heikkilä, P.; Pukkala, E. Occupational exposure to diesel and gasoline engine exhausts and risk of lung cancer among Finnish workers. *Amer. J. Ind. Med.* **2004**, *45*, 483–490.

7. Bergdahl, I.A.; Jonsson, H.; Eriksson, K.; Damber, L.; Järvholm, B. Lung cancer and exposure to quartz and diesel exhaust in Swedish iron ore miners with concurrent exposure to radon. *Occup. Environ. Med.* **2010**, *67*, 513–518.
8. Neumeyer-Gromen, A.; Razum, O.; Kersten, N.; Seidler, A.; Zeeb, H. Diesel motor emissions and lung cancer mortality—Results of the second follow-up of a cohort study in potash miners. *Int. J. Cancer* **2009**, *124*, 1900–1906.
9. Attfield, M.D.; Schleiff, P.L.; Lubin, J.H.; Blair, A.; Stewart, P.A.; Vermeulen, R.; Coble, J.B.; Silverman, D.T. The diesel exhaust in miners study: A cohort mortality study with emphasis on lung cancer. *J. Nat. Cancer Inst.* **2012**, *104*, 869–883.
10. Garshick, E.; Laden, F.; Hart, J.E.; Smith, T.J.; Rosner, B. Smoking imputation and lung cancer in railroad workers exposed to diesel exhaust. *Amer. J. Ind. Med.* **2006**, *49*, 709–718.
11. Garshick, E.; Laden, F.; Hart, J.E.; Rosner, B.; Davis, M.E.; Eisen, E.A.; Smith, T.J. Lung cancer and vehicle exhaust in trucking industry workers. *Environ. Health Perspect.* **2008**, *116*, 1327–1332.
12. Larkin, E.K.; Smith, T.J.; Stayner, L.; Rosner, B.; Speizer, F.E.; Garshick, E. Diesel exhaust exposure and lung cancer: Adjustment for the effect of smoking in a retrospective cohort study. *Amer. J. Ind. Med.* **2000**, *38*, 399–409.
13. Garshick, E.; Schenker, M.B.; Munoz, A.; Segal, M.; Smith, T.J.; Woskie, S.R.; Hammond, S.K.; Speizer, F.E. A retrospective cohort study of lung cancer and Diesel exhaust exposure in railroad workers. *Am. Rev. Respir. Dis.* **1988**, *137*, 820–825.
14. Crump, K.S. Lung cancer mortality and diesel exhaust: Reanalysis of a retrospective cohort study of U.S. railroad workers. *Inhal. Toxicol.* **1999**, *11*, 1–17.
15. Ahlberg, J.; Ahlbom, A.; Lipping, H.; Norell, S.; Osterblom, L. Cancer in professional drivers-problem-orientated registry study. *Lakartidningen* **1981**, *78*, 1545–1546.
16. Balarajan, R.; McDowall, M.E. Professional drivers in London: A mortality study. *Brit. J. Ind. Med.* **1988**, *45*, 483–486.
17. Bender, A.P.; Parker, D.L.; Johnson, R.A.; Scharber, W.K.; Williams, A.N.; Marbury, M.C.; Mandel, J.S. Minnesota highway maintenance worker study: Cancer mortality. *Amer. J. Ind. Med.* **1989**, *15*, 545–556.
18. Boffetta, P.; Dosemeci, M.; Gridley, G.; Bath, H.; Moradi, T.; Silverman, D. Occupational exposure to diesel engine emissions and risk of cancer in Swedish men and women. *Cancer Cause. Control* **2001**, *12*, 365–374.
19. Garshick, E.; Laden, F.; Hart, J.E.; Rosner, B.; Smith, T.J.; Dockery, D.W.; Speizer, F.E. Lung cancer in railroad workers exposed to diesel exhaust. *Environ. Health Perspect.* **2004**, *112*, 1539–1543.
20. Guberan, E.; Usel, M.; Raymond, L.; Bolay, J.; Fioretta, G.; Puissant, J. Increased risk for lung cancer and for cancer of the gastrointestinal tract among Geneva professional drivers. *Brit. J. Ind. Med.* **1992**, *49*, 337–344.
21. Gustafsson, L.; Wall, S.; Larsson, L.G.; Skog, B. Mortality and cancer incidence among Swedish dock workers—A retrospective cohort study. *Scand. J. Work Environ. Health* **1986**, *12*, 22–26.
22. Haldorsen, T.; Andersen, A.; Boffetta, P. Smoking-adjusted incidence of lung cancer by occupation among Norwegian men. *Cancer Cause. Control* **2004**, *15*, 139–147.

23. Hansen, E.S. A follow-up study on the mortality of truck drivers. *Amer. J. Ind. Med.* **1993**, *23*, 811–821.
24. Howe, G.R.; Fraser, D.; Lindsay, J.; Presnal, B.; Yu, S.Z. Cancer mortality (1965–1977) in relation to diesel fume and coal exposure in a cohort of retired railway workers. *J. Nat. Cancer Inst.* **1983**, *70*, 1015–1019.
25. Jakobsson, R.; Gustavsson, P.; Lundberg, I. Increased risk of lung cancer among male professional drivers in urban but not rural areas of Sweden. *Occup. Environ. Med.* **1997**, *54*, 189–193.
26. Järvholm, B.; Silverman, D. Lung cancer in heavy equipment operators and truck drivers with diesel exhaust exposure in the construction industry. *Occup. Environ. Med.* **2003**, *60*, 516–520.
27. Kaplan, I. Relationship of noxious gases to carcinoma of the lung in railroad workers. *J. Am. Med. Assn.* **1959**, *171*, 2039–2043.
28. Laden, F.; Hart, J.E.; Smith, T.J.; Davis, M.E.; Garshick, E. Cause-specific mortality in the unionized U.S. trucking industry. *Environ. Health Perspect.* **2007**, *115*, 1192–1196.
29. Lagorio, S.; Forastiere, F.; Bargagli, A.M.; Iavarone, I.; Vanacore, N.; Borgia, P.; Perucci, C.A. Cohort Mortality Study of Filling Station Attendants. In Proceedings of the 9th International Symposium in Epidemiology in Occupational Health, International Commission on Occupational Health (ICOH), Cincinnati, OH, USA, 23–25 September 1992.
30. Luepker, R.; Smith, M. Mortality in unionized truck drivers. *J. Occup. Med.* **1978**, *20*, 677–682.
31. Magnani, C.; Pannett, B.; Winter, P.D.; Coggon, D. Application of a job-exposure matrix to national mortality statistics for lung cancer. *Brit. J. Ind. Med.* **1988**, *45*, 70–72.
32. Maizlish, N.; Beaumont, J.; Singleton, J. Mortality among Californian highway workers. *Amer. J. Ind. Med.* **1988**, *13*, 363–379.
33. Menck, H.R.; Henderson, B.E. Occupational differences in rates of lung cancer. *J. Occup. Med.* **1976**, *18*, 797–801.
34. Milham, S. *Occupation Mortality in Washington State, 1950–1971*; National Institute for Occupational Savety and Health (NIOSH): Cininnati, OH, USA, 1983.
35. Netterstrom, B. Cancer incidence among urban bus drivers in Denmark. *Int. Arch. Occup. Environ. Health* **1988**, *61*, 217–221.
36. Säverin, R.; Bräunlich, A.; Dahmann, D.; Enderlein, G.; Heuchert, G. Diesel exhaust and lung cancer mortality in potash mining. *Amer. J. Ind. Med.* **1999**, *36*, 415–422.
37. Nokso-Koivisto, P.; Pukkala, E.; Past exposure to asbestos and combustion products and incidence of cancer among Finnish locomotive drivers. *Occup. Environ. Med.* **1994**, *51*, 330–334.
38. Paradis, G.; Theriault, G.; Tremblay, C. Mortality in a historical cohort of bus drivers. *Int. J. Epidemiol.* **1989**, *18*, 397–402.
39. Pukkala, E.; Teppo, L.; Hakulinen, T.; Rimpelä, M. Occupation and smoking as risk determinants of lung cancer. *Int. J. Epidemiol.* **1983**, *12*, 290–296.
40. Raffle, P.A.B. The health of the worker. *Br. J. Ind. Med.* **1957**, *14*, 73–80.
41. Raffnson, V.; Johannesdottir, S.G.; Oddsson, H.; Benediktsson, H.; Tulinius, H.; Magnússon, G. Mortality and cancer incidence among marine engineers and machinists in Iceland. *Scand. J. Work Environ. Health* **1988**, *14*, 197–200.

42. Rafnsson, V.; Gunnarsdottir, H. Mortality among professional drivers. *Scand. J. Work Environ. Health* **1991**, *17*, 312–317.
43. Rushton, L.; Alderson, M.R.; Nagarajah, C.R. Epidemiological survey of maintenance workers in London transport executive bus garages and Chiswick works. *Brit. J. Ind. Med.* **1983**, *40*, 340–345.
44. Schenker, M.B.; Smith, R.; Munoz, A.; Woskie, S.; Spezier, F.E. Diesel exposure and mortality among railroad workers: Results of a pilot study. *Brit. J. Ind. Med.* **1984**, *41*, 320–327.
45. Stern, F.B.; Curtis, R.A.; Lemen, R.A. Exposure of motor vehicle examiners to carbon monoxide: A historical prospective mortality study. *Arch. Environ. Health* **1981**, *36*, 59–66.
46. Stern, F.; Haring-Sweeney, M. Proportionate mortality among unionized construction operating engineers. *Amer. J. Ind. Med.* **1997**, *32*, 51–65.
47. Waller, R.E. Trends in lung cancer in London in relation to exposure to diesel fumes. *Environ. Int.* **1981**, *5*, 479–483.
48. Waxweiler, R.J.; Wagoner, J.K.; Archer, V.E. Mortality of potash workers. *J. Occup. Med.* **1973**, *15*, 486–489.
49. Wong, O.; Morgan, R.K.; Kheifets, L.; Larson, S.R.; Whorton, M.D. Mortality among members of a heavy construction equipment operators union with potential exposure to diesel exhaust emission. *Brit. J. Ind. Med.* **1985**, *42*, 435–448.
50. Möhner, M.; Kersten, N.; Gellissen, J. Zum Einfluss von Dieselmotoremissionen auf das Lungenkrebsrisiko—Reanalyse einer Kohortenstudie im Kalibergbau. In Proceedings of the 6th Annual Conference of the German Society for Epidemiology (DGEpi), Mainz, Germany, 26–29 September 2011; pp. 734–735.
51. Möhner, M.; Kersten, N.; Gellissen, J. Diesel motor exhaust and lung cancer mortality: Reanalysis of a cohort study in potash miners. *Eur. J. Epidemiol.* **2013**, *28*, 159–168.
52. Silverman, D.T.; Samanic, C.M.; Lubin, J.H.; Blair, A.E.; Stewart, P.A.; Vermeulen, R.; Coble, J.B.; Rothman, N.; Schleiff, P.L.; Travis, W.D.; *et al*. The diesel exhaust in miners study: A nested case-control study of lung cancer and diesel exhaust. *J. Nat. Cancer Inst.* **2012**, *104*, 855–868.
53. Morfeld, P. Diesel exhaust in miners study: How to understand the findings? *J. Occup. Med. Toxicol.* **2012**, *10*, doi:10.1186/1745-6673-7-10.
54. Gamble, J.F.; Nicolich, M.J.; Boffetta, P. Lung cancer and diesel exhaust: An updated critical review of the occupational epidemiology literature. *Crit. Rev. Toxicol.* **2012**, *42*, 549–598.
55. Emmelin, A.; Nyström, L.; Wall, S. Diesel exhaust exposure and smoking: A case-referent study of lung cancer among Swedish dock workers. *Epidemiology* **1993**, *4*, 237–244.
56. Gustavsson, P.; Plato, N.; Lidstrom, E.B.; Hogstedt, C. Lung cancer and exposure to diesel exhaust among bus garage workers. *Scand. J. Work Environ. Health* **1990**, *16*, 348–354.
57. Gustavsson, P.; Jakobsson, R.; Nyberg, F.; Pershagen, G.; Järup, L.; Schéele, P. Occupational exposure and lung cancer risk: A population-based case-referent study in Sweden. *Amer. J. Epidemiol.* **2000**, *152*, 32–40.
58. Villeneuve, P.J.; Parent, M.É.; Sahni, V.; Johnson, K.C. Canadian Cancer Registries Epidemiology Research Group. Occupational exposure to diesel and gasoline emissions and lung cancer in Canadian men. *Environ. Res.* **2011**, *111*, 727–735.

59. Benhamou, S.; Benhamou, E.; Flamant, R. Occupational risk factors of lung cancer in a French case-control study. *Brit. J. Ind. Med.* **1988**, *45*, 231–233.
60. Boffetta, P.; Harris, R.E.; Wynder, E.L. Case-control study on occupational exposure to diesel exhaust and lung cancer risk. *Amer. J. Ind. Med.* **1990**, *17*, 577–591.
61. Brüske-Hohlfeld, I.; Möhner, M.; Ahrens, W.; Pohlabeln, H.; Heinrich, J.; Kreuzer, M.; Jöckel, K.H.; Wichmann, H.E. Lung cancer risk in male workers occupationally exposed to diesel motor emissions in Germany. *Amer. J. Ind. Med.* **1999**, *36*, 405–414.
62. Buiatti, E.; Kriebel, D.; Geddes, M.; Santucci, M.; Pucci, N. A case control study of lung cancer in Florence, Italy. I. Occupational risk factors. *J. Epidemiol. Community Health* **1985**, *39*, 244–250.
63. Burns, P.B.; Swanson, G.M. The Occupational Cancer Incidence Surveillance Study (OCISS): Risk of lung cancer by usual occupation and industry in the Detroit metropolitan area. *Amer. J. Ind. Med.* **1991**, *19*, 655–671.
64. Coggon, D.; Pannett, B.; Acheson, E.D. Use of job-exposure matrix in an occupational analysis of lung and bladder cancers on the basis of death certificates. *J. Nat. Cancer Inst.* **1984**, *72*, 61–65.
65. Damber, L.A.; Larsson, L.G. Occupation and male lung cancer: A case-control study in northern Sweden. *Brit. J. Ind. Med.* **1987**, *44*, 446–453.
66. Decoufle, P.; Stanislawczyk, K.; Houten, L.; Bross, J.D.J.; Viadana, E. *A Retrospective Survey of Cancer in Relation to Occupation*; DHEW (NIOSH), Department of Health, Education and Welfare: Cincinnati, OH, USA, 1977.
67. Elci, O.C.; Akpinar-Elci, M.; Alavanja, M.; Dosemeci, M. Occupation and the risk of lung cancer by histologic types and morphologic distribution: A case control study in Turkey. *Monaldi Arch. Chest Dis.* **2003**, *59*, 183–188.
68. Garshick, E.; Schenker, M.B.; Munoz, A.; Segal, M.; Smith, T.J.; Woskie, S.R.; Hammond, S.K.; Speizer, F.E. A case-control study of lung cancer and Diesel exhaust exposure in railroad workers. *Am. Rev. Respir. Dis.* **1987**, *135*, 1242–1248.
69. Hall, N.E.; Wynder, E.L. Diesel exhaust exposure and lung cancer: A case—Control study. *Environ. Res.* **1984**, *34*, 77–86.
70. Hansen, J.; Raaschou-Nielsen, O.; Olsen, J.H. Increased risk of lung cancer among different types of professional drivers in Denmark. *Occup. Environ. Med.* **1998**, *55*, 115–118.
71. Hayes, R.B.; Thomas, T.; Silverman, D.T.; Vineis, P.; Blot, W.J.; Mason, T.J.; Pickle, L.W.; Correa, P.; Fontham, E.T.; Schoenberg, J.B. Lung cancer in motor exhaust-related occupations. *Amer. J. Ind. Med.* **1989**, *16*, 685–695.
72. Kauppinen, T.P.; Partanen, T.J.; Hernberg, S.G.; Nickels, J.I.; Luukkonen, R.A.; Hakulinen, T.R.; Pukkala, E.I. Chemical exposures and respiratory cancer among Finnish woodworkers. *Brit. J. Ind. Med.* **1993**, *50*, 143–148.
73. Lerchen, M.L.; Wiggins, C.L.; Samet, J.M. Lung cancer and occupation in New Mexico. *J. Nat. Cancer Inst.* **1987**, *79*, 639–645.
74. Milne, K.L.; Sandler, D.P.; Everson, R.E.; Brown, S.M. Lung cancer and occupation in Alameda County: A death certificate case-control study. *Amer. J. Ind. Med.* **1983**, *4*, 565–575.

75. Olsson, A.C.; Gustavsson, P.; Kromhout, H.; Peters, S.; Vermeulen, R.; Brüske, I.; Pesch, B.; Siemiatycki, J.; Pintos, J.; Brüning, T.; *et al*. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. *Amer. J. Respir. Crit. Care Med.* **2011**, *183*, 941–948.
76. Parent, M.E.; Rousseau, M.C.; Boffetta, P.; Cohen, A.; Siemiatycki, J. Exposure to diesel and gasoline engine emissions and the risk of lung cancer. *Amer. J. Epidemiol.* **2007**, *165*, 53–62.
77. Pfluger, D.H.; Minder, C.E. A mortality study of lung cancer among Swiss professional drivers: Accounting for the smoking related fraction by a multivariate approach. *Soz Präventivmed* **1994**, *39*, 372–378.
78. Richiardi, L.; Mirabelli, D.; Calisti, R.; Ottino, A.; Ferrando, A.; Boffetta, P.; Merletti, F. Occupational exposure to diesel exhausts and risk for lung cancer in a population-based case-control study in Italy. *Ann. Oncol.* **2006**, *17*, 1842–1847.
79. Siemiatycki, J.; Gerin, M.; Stewart, P.; Nadon, L.; Dewar, R.; Richardson, L. Association between several sites of cancer and ten types of exhaust and combustion products. *Scand. J. Work Environ. Health* **1988**, *14*, 79–90.
80. Soll-Johanning, H.; Bach, E.; Jensen, S.S. Lung and bladder cancer among Danish urban bus drivers and tramway employees: A nested case-control study. *Occup. Med. (Lond.)* **2003**, *53*, 25–33.
81. Steenland, N.K.; Silverman, D.T.; Hornung, R.W. Case-control study of lung cancer and truck driving in the Teamster Union. *Amer. J. Public Health* **1990**, *80*, 670–674.
82. Swanson, G.M.; Lin, C.S.; Burns, P.B. Diversity in the association between occupation and lung cancer among black and white men. *Cancer Epidemiol. Biomarkers Prev.* **1993**, *2*, 313–320.
83. Wegman, D.H.; Peters, J.M. Oat cell lung cancer in selected occupations: A case-control study. *J. Occup. Med.* **1978**, *20*, 793–796.
84. Steenland, K. Lung cancer and diesel exhaust: A review. *Amer. J. Ind. Med.* **1986**, *20*, 177–189.
85. Dawson, S.V.; Alexeeff, G.V. Multi-stage model estimates of lung cancer risk from exposure to diesel exhaust, based on a U.S. railroad worker cohort. Response to commentary. *Risk Anal.* **2001**, *21*, 213–216.