**Diesel Engine Exhaust Exposure, Smoking, and Lung Cancer Subtype Risks. A Pooled Exposure-Response Analysis of 14 Case-Control Studies**

# Diesel Engine Exhaust Exposure, Smoking, and Lung Cancer Subtype Risks A Pooled Exposure–Response Analysis of 14 Case–Control Studies

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## Abstract

Rationale: Although the carcinogenicity of diesel engine exhaust has been demonstrated in multiple studies, little is known regarding exposure–response relationships associated with different exposure subgroups and different lung cancer subtypes.

Objectives: Weexpanded on a previous pooled case–control analysis on diesel engine exhaust and lung cancer by including three additional tudies and quantitative exposure assessment to evaluate lung cancer nd subtype risks associated with occupational exposure to diesel exhaust characterized by elemental carbon (EC) concentrations.

Methods:We usedaquantitativeECjob-exposurematrix for exposure assessment. Unconditional logistic regression models were used to calculate lung cancer odds ratios and 95% confidence intervals (CIs) associated with various metrics of EC exposure. Lung cancer excess lifetime risks (ELR) were calculated using life tables accounting for allcause mortality. Additional stratified analyses by smoking history and lung cancer subtypes were performed in men.

Measurements and Main Results: Our study included 16,901 lung cancer cases and 20,965 control subjects. In men, exposure response between EC and lung cancer was observed: odds ratios ranged from 1.09 (95% CI, 1.00–1.18) to 1.41 (95% CI, 1.30–1.52) for the lowest and highest cumulative exposure groups, respectively. EC-exposed men had elevated risks in all lung cancer subtypes investigated; associations were strongest for squamous and small cell carcinomas and weaker for adenocarcinoma. EC lung cancer exposure response was observed in men regardless of smoking history, including in never-smokers. ELR associated with 45 years of EC exposure at 50, 20, and 1 mg/m$^3$ were 3.0%, 0.99%, and 0.04%, respectively, for both sexes combined.

Conclusions: We observed a consistent exposure–response relationship betweenECexposure and lung cancer in men. Reduction of workplace EC levels to background environmental levels will further reduce lung cancer ELR in exposed workers.

Keywords: occupational exposure; diesel exhaust; lung neoplasms; epidemiology

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## At a Glance Commentary

Scientific Knowledge on the Subject: Diesel engine exhaust is classified as a group 1 human carcinogen by the International Agency for Research on Cancer. Multiple studies have reported positive exposure–response relationships between occupational elemental carbon exposure and lung cancer.

What This Study Adds to the Field: In our large pooled analysis of case–control studies, we report a consistent exposure–response relationship between occupational diesel exhaust exposure and lung cancer in men. Increased lung cancer risks were found in elemental carbon–exposed men

who were never-smokers and smokers. Increased risks in exposed men were also observed for all lung cancer subtypes included; the observed associations were the strongest for squamous cell and small cell carcinomas and weaker for adenocarcinoma.

The International Agency for Research on Cancer (IARC) classifies diesel engine exhaust (hereafter diesel exhaust) as a group 1human carcinogen (1). Previous studies have provided consistent epidemiological evidence that lung cancer is associated with occupational exposure to diesel exhaust (2–5). Positive exposure–response relationships of diesel exhaust exposure and lung cancer were also reported by studies with quantitative exposure assessment for elemental carbon (EC), which is a measure of diesel exhaust exposure (4–7). However, few studies have explored the risk of lung cancer associated with low
exposure levels, and none have observed a positive association at lifetime cumulative EC exposure levels below 50 mg/m3-years. Questions also remain regarding the role of cigarette smoking as a potential confounder or effect modifier in the relationship between EC exposure and lung cancer. For instance, although a handful of studies have shown suggestive elevated lung cancer risks in diesel exhaust–exposed workers who were never-smokers (2, 8, 9), only one study reported a significant effect (4). The same study also reported attenuated lung cancer risk in subjects who were heavy smokers and
highly exposed to diesel exhaust (i.e., a negative interaction). Finally, results reported by studies on risks of major lung
cancer subtypes associated with diesel exhaust exposure have been inconsistent.
Some studies reported the strongest association in large cell carcinoma compared with other major lung cancer subtypes (2, 9),
whereas others observed higher risks in squamous cell carcinoma (8, 10). Previously, we published a study with pooled subjects from 11 lung cancer case–control studies from Europe and Canada (3). In the current study, we increased the study population by including three additional studies (3,663 cases; 4,805 controls). Occupational exposure assessment was also enhanced with the use of a new job-exposure matrix (JEM), in which EC exposure was estimated quantitatively based on subject occupations. The purposes of our work were to evaluate 1) the lung cancer risks associated with various indices of
occupational diesel exhaust exposure by sex; 2) the associations between diesel exhaust exposure and lung cancer by smoking status and cancer subtype in men; 3) the joint effects of diesel exhaust exposure and smoking on the risk of lung cancer and its major subtypes on the additive and multiplicative scale in men; and 4) the excess lifetime lung cancer risks associated with various levels of occupational diesel exhaust exposure in both sexes combined.

## Methods

### Study Population

Subjects from 14 hospital- and population-based lung cancer case–control studies in 13 European countries and Canada were pooled. A detailed description of the original study population is available elsewhere (3). The current study updated the population with 3,663 cases and 4,805 controls from the TORONTO, CAPUA (Cáncer de Pulmón en Asturias), and ICARE (Investigation of Occupational and Environmental Causes of Respiratory Cancers) studies in Canada, Spain, and France, respectively (Table E1 in the online supplement). The project received ethical approvals from all participating countries and from the IARC institutional review board. More information about the SYNERGY project is available online at http://synergy.iarc.fr.

### Job-Exposure Matrix and Exposure Assessment

A quantitative diesel engine exhaust JEM (DEE-JEM) was developed by C.G. and R.V. The DEE-JEM consists of EC exposure (in mg/$m^3$) assigned to all 1,506 five-digit International Standard

Classification of Occupations (ISCO) (version 1968 or ISCO-68) (11) and was constructed based on 4,417 occupational EC measurements (data sources available in the online supplement Methods and Table E6). For occupations represented in the EC exposure measurements, the mean exposure concentrations were directly assigned. For occupations without measurement data, exposure concentrations from similar occupations with measurement data were assigned using expert decisions. An exposure probability factor was also assigned by expert decision to each exposed job (details on probability factors available in Methods in the online supplement). The DEE-JEM was linked to study participant job histories by ISCO-68 occupations. Probability-weighted cumulative EC exposure (hereafter cumulative EC, expressed in $mg/m^3$-years) was calculated as the sum of the product of exposure levels, probabilities, and duration (in years) across all reported job periods for each subject. The DEE-JEM is available upon request from the corresponding author.

Main Statistical Analysis

Separately for men and women, unconditional logistic regression models were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of lung cancer associated with various categorical EC exposure metrics, including ever/never exposure, duration of exposure ( 10, 10–19, 20–29, and  29 yr), and cumulative exposure (quartiles of exposure distribution among controls:  0–22, 23–70, 71–178,  178 $mg/m^3$-years). Trends were assessed using *P* values from the respective indices of EC exposure as continuous variables for all subjects and for exposed subjects only. Adjustments for the main analyses were determined *a priori* within the SYNERGY consortium and were identical with our previous occupational exposure publications (3, 12); these adjustments included study, age group ( 45, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and  74 yr), smoking [log(cigarette pack- years 1 1)], smoking cessation prior to interview/diagnosis (current smokers;  0–7, 8–15, 16–25, and  25 yr; and never- smokers), and having been ever employed in occupations with known lung cancer risks (list A jobs ever/never; full list in Table E7). First published in 1982, list A jobs include occupations with definite lung cancer risks according to the IARC Monographs; the list was updated in 1995 and 2000 to cover all IARC-reviewed agents up to volume 75 of the Monographs (13, 14). Smokers were defined as smoking more than one cigarette per day for more than 1 year. Smoking pack-years were calculated by summing the products of average daily smoking amount in 20- cigarette packs and smoking duration in years. Association between lung cancer and cumulative EC exposure as a continuous metric was assessed with a logistic linear regression model for men, women, and all subjects with identical adjustments as the categorical models.

Models with various cumulative EC exposure lag times (i.e., omitting exposure in the last 5, 10, 15, or 20 years, or no omission at all) were constructed. According to minimized Akaike information criterion value, model fit was the best when lag time was 10 years—therefore, only results from models with a 10-year lag are presented.

Using the lung cancer risk from our linear continuous exposure model with all subjects, we calculated lung cancer excess lifetime risks (ELRs) at age 80 associated with 45 years of occupational EC exposure at 50, 20, and 1 $mg/m^3$ using life-table methods accounting for all-cause mortality outlined by Vermeulen and colleagues (7). The selected exposure levels at 50, 20, and 1 $mg/m^3$ represented recommended limit values from the following: *1*) the German Committee for Hazardous Substances in 2017 based on a study on lung irritation after controlled human exposure (15); *2*) the U.S. National Institute of Occupational Safety and Health in 2003 that was later withdrawn (16); and *3*) the Health Council of the Netherlands in 2019 based on exposure–response estimates from Vermeulen and colleagues (7, 17), respectively. 2008 European data on mortality from all causes and lung cancer were used in our calculations (18).

Extended Analysis for Male Subjects To further investigate the exposure–response relationship between EC exposure and lung cancer in men, stratified analyses were performed to calculate lung cancer ORs associated with cumulative EC exposure categories with different major lung cancer subtypes and smoking histories. In addition, nonparametric thin-plate regression splines were created, as implemented in the R package mgcv, to visualize the

shape of the exposure–response relationships between EC exposure and lung cancer subtypes in men. The number of basis functions was limited to three ($k$ = 3), and the smoothing parameter was estimated using the relative maximum likelihood method. Spline model results were truncated at the 99th percentile of EC exposure to emphasize results with greater data support.

Additive interactions of cigarette smoking and EC exposure on lung cancer and subtype risks in men were assessed by calculating the excess risks due to interaction (RERI) using ORs from our logistic models as defined by Rothman and Greenland (19) and as implemented in the epi.interaction package in R. RERI values measure departure from additivity, with 0 representing no interaction on the additive scale (20). Interactions in men on the multiplicative scale were assessed using $P$ values obtained from the cross products of smoking and EC exposure in the adjusted logistic models.

Statistical analyses were conducted using SAS (version 9.3; SAS Institute) and R (version 3.6).

## Results

A total of 37,866 subjects (16,901 cases; 20,965 controls) were included in our final analyses (Table 1). Among the lung cancer cases there were 4,752 adenocarcinomas, 810 large cell carcinomas, 2,730 small cell carcinomas, 6,503 squamous cell carcinomas, 2,012 other lung cancers, and 94 cases without subtype information.

In men, we observed elevated ORs for subjects with ever occupational exposure to EC (OR, 1.22; 95% CI, 1.15–1.29; Table 2).

Increasing trends in lung cancer risks in men were associated with increases in both exposure duration and cumulative exposure ($P$ trends < 0.01). Elevated male lung cancer ORs were also observed in the lowest categories of exposure duration (1–9 yr; OR, 1.07; 95% CI, 1.00–1.16) and cumulative exposure (0–22 mg/m$^3$-years; OR, 1.09; 95% CI, 1.00–1.19). In our female population, we observed no associations between lung cancer and different EC exposure metrics. Our continuous EC exposure models show that a 1 mg/m$^3$-year increase in cumulative exposure was associated with an increase in lung cancer OR by a factor of 1.00001 (95% CI, 0.9987–1.00131) for women. The corresponding results for men and for all subjects were identical: lung cancer OR increased by a factor of 1.00034 (95% CI, 1.00021–1.00048) per mg/m$^3$-years increase in cumulative EC exposure. Lung cancer ELRs associated with lifetime occupational EC exposure at 50, 20, and 1 mg/m$^3$ were 3.0%, 0.99%, and 0.04%, respectively, for both sexes combined.

By lung cancer subtype, increasing cumulative EC exposure was associated with increasing ORs of squamous cell ($P$ trend < 0.01) and small cell carcinomas ($P$ trend 0.02) in men (Table 3). For squamous cell carcinoma, all categories of cumulative EC exposure were associated with elevated ORs in men, including the lowest exposure (OR, 1.13; 95% CI, 1.01–1.26). The highest risks for both adenocarcinoma (OR, 1.23; 95% CI, 1.09–1.39) and large cell carcinoma (OR, 1.31; 95% CI, 1.02–1.67) were also observed in men in the group with the highest exposure.

Results from the nonparametric spline analyses for male subjects show monotonic increases in cancer risks for overall lung cancer and all four of the included subtypes (Figure 1). Among the lung cancer subtypes, squamous cell and small cell carcinomas show the strongest association with cumulative EC exposure, followed by large cell carcinoma and adenocarcinoma.

In our analyses stratified by smoking status, exposure–response associations between cumulative EC exposure and lung cancer were observed in men regardless of smoking history (Table 4). Lung cancer risks were similar for men in the highest EC exposure group who were never-smokers (OR, 1.41; 95% CI, 1.04–1.88), former smokers (OR, 1.47; 95% CI, 1.31–1.65), and current smokers (OR, 1.40; 95% CI, 1.24–1.57).

Superadditive joint effects of smoking and EC exposure were observed in men for overall lung cancer and for all four cancer subtypes (Table 5). Suggestive super- multiplicative joint

effects of smoking and EC exposure were observed for large cell carcinoma in men ($P = 0.05$).

## Discussion

In a large pooled case–control population, we observed positive associations between lung cancer and different occupational EC exposure metrics, including ever EC exposure, exposure duration, and cumulative exposure, in men. Increasing exposure duration and cumulative exposure were associated with increases in lung cancer risks in men, exhibiting monotonic exposure–response relationships. Our results are in accordance with, and further expand on, results from our earlier analysis within the SYNERGY study with 11 studies and semiquantitative exposure assessment, in which we reported a consistent exposure–response relationship between lung cancer and EC exposure (3).

Additional evidence of the exposure–response relationship between diesel exhaust exposure and lung cancer is provided by studies on workers in highly exposed industries such as mining (4, 21–23) and trucking (5, 6).

In a metaregression analysis of the exposure–response relationship of lung cancer and diesel exhaust exposure based on data from three occupational cohort studies, Vermeulen and colleagues estimated that each mg/m$^3$-year increase in cumulative EC exposure results in a lung cancer relative risk (RR) of 1.00098 (7). A subsequent sensitivity analysis reported a range of lung cancer RR of 1.0006 to 1.0012 per mg/m$^3$-years increase in cumulative EC exposure from several alternative models (24). These exposure–response slope estimates are approximately 2–3 times higher than our present linear model estimate of 1.00034 for all subjects. This difference may be due to factors such as occupational cohorts having higher cumulative EC exposures and more accurate exposure assessment in specific industries. Despite the differences on the exact risk magnitude, a consistent exposure–response trend between occupational diesel exhaust exposure and lung cancer was reported by studies with different designs among different populations.

We did not observe an exposure threshold for diesel exhaust–related lung cancer in men within the cumulative EC exposure ranges we investigated; increased lung cancer risk in men was observed in the lowest cumulative EC exposure group, with a median exposure of 11 mg/m$^3$-years.

An additional sensitivity analysis with 10 cumulative exposure groups suggested (naturally, with less precision) an increased risk among the lowest exposure group with a median EC exposure of 3.3 mg/m$^3$-years (Table E2). Few other studies investigated lung cancer risks in similar cumulative EC exposure ranges quantitatively. In occupational cohorts with higher EC exposures, one study reported a lung cancer OR of 1.31 (95% CI, 1.01–1.71) in U.S. trucking workers with a cumulative exposure of approximately 51 mg/m –year (6), whereas another study reported a lung cancer OR of 0.74 (95% CI, 0.40–1.38) for U.S. miners with a cumulative EC exposure around 37 mg/m$^3$-years (4).

We found that diesel exhaust exposure was associated with all four major lung differential risks were observed by subtype. Both our logistic regression and spline models showed that the associations were the strongest for squamous cell and small cell carcinomas, moderate for large cell carcinoma, and weakest for adenocarcinoma. Similar findings supportive of a stronger link between diesel exhaust exposure and lung squamous cell carcinoma were reported in populations in Canada (8–10), Finland (25), and Sweden (2, 26). This is the first report of a positive exposure–response relationship for diesel exhaust exposure and lung small cell carcinoma in men.

Guo and colleagues observed a small cell carcinoma OR of 2.31 (95% CI, 1.02–5.25) for female Finnish workers in the low diesel exhaust exposure category based on six exposed cases (25). Elevated point estimates of small cell carcinoma risks were also observed in population-based studies from different countries (2, 10, 25). For adenocarcinoma, in accordance with our current observations, previous studies were consistent in reporting ORs that were lower than overall lung cancer risks (2, 8–10, 25, 26). Information on the risk of large cell carcinoma related to diesel exhaust exposure is limited; only two previous studies included large cell carcinoma in subtype analyses (2, 9). These studies reported exposure–response relationships for duration, intensity, and lifetime cumulative exposure to diesel exhaust and large cell carcinoma. In our

male population, we observed a clear increased large cell carcinoma risk only in the group with the highest cumulative EC exposure ( ≥ 178 mg/m$^3$-years), with a suggestive elevated OR estimate for the second highest exposed group.

We observed a lung cancer exposure–response risk trend in never- smoking men who were exposed to EC. Similarly, Silverman and colleagues reported a significant lung cancer OR of 7.30 (95% CI, 1.46–36.57) among highly exposed U.S. miners who never smoked (4). The very high risk observed in the U.S. miners may be attributable to higher cumulative EC exposure in mining occupations or the fact that the estimate was based on only seven exposed cases.

The observed superadditive joint effects between EC exposure and smoking for overall lung cancer and its subtypes in men indicate that the absolute risk of cancer for men exposed to both EC and smoking was higher than the sum of the absolute risks of cancer from EC exposure and smoking alone (27). Only one other study in Swedish dock workers investigated EC and smoking interaction on the additive scale and similarly reported a superadditive effect (28). Interaction in other studies was assessed on the multiplicative scale, in which supermultiplicative interaction represents a scenario in which the risk ratios (e.g., OR) of cancer for those exposed to both EC and smoking was higher than the product of the cancer risk ratios from EC exposure and smoking alone (27). In two nonoverlapping Canadian population- based case–control studies, no significant multiplicative interaction was observed (9, 10). Lastly, in the U.S. Miners Study, Silverman and colleagues reported a suggestive submultiplicative interaction, in which high exposure to both EC and cigarette smoke resulted in an attenuation of lung cancer risk increase (4). In additional analyses wherein we explored cancer risks in four groups of male smokers ( < 10, 10–19, 20–39, and ≥ 39 pack-years, respectively) with cumulative EC exposures similar to those in Silverman and colleagues, we did not observe submultiplicative interactive effects and found consistent risk increases across all EC exposure categories for subjects with increasing pack-years of smoking (Table E3).

Strengths of our study include a large pooled population with detailed smoking and occupational histories. Our sample size allowed for stratified analyses to explore the exposure–response relationship in different subgroups, whereas high-quality smoking and occupational histories allowed for the control of important potential confounders such as smoking and exposure to other occupational carcinogens. Exposure assessment was performed with a quantitative JEM developed using a combination of exposure measurements and expert assessment. The current DEE- JEM was developed independently from the Domtoren-JEM (DOM-JEM), an expert judgment JEM we used in an earlier analysis (3). Despite this difference, results of both analyses showed consistent exposure–response relationships between occupational exposure to diesel exhaust and lung cancer. Reliability studies on occupational exposure assessment also suggested that incorporating measurements in the exposure assessment process may improve expert judgment (29, 30). Finally, the exposure–response relationship between EC exposure and lung cancer in our male population was robust and present in various sensitivity analyses, including when we limited analyses to a more homogeneous group of studies, when we limited our analyses to blue-collar workers only, and when we assessed EC exposure with alternative JEM configurations (Tables E4.1–E4.9).

There are also limitations in our work. Our DEE-JEM did not account for changes in exposure at different time periods and therefore may underestimate exposure for earlier periods when exposure was likely higher (31). The EC measurements used in our JEM were collected from 1985 to 2016 (median, 2002), whereas our subjects were assessed as exposed from 1923 to 2020 (median, 1968). However, the association between EC exposure and lung cancer was still present when we restricted our analyses to subjects exposed after 1960 (Table E4.2). Because list A jobs included some jobs with potential diesel exhaust exposure, adjustment for ever-employment in any list A jobs in our main model may represent overadjustment for coexposures to other lung carcinogens. Removing all jobs with EC exposure from list A, however, may lead to underadjustment because many EC-exposed jobs have concurrent

exposures to other lung carcinogens. We explored the coexposure adjustments using two additional sensitivity models: one with no adjustment and another adjusting for ever exposure to crystalline silica, asbestos, polycyclic aromatic hydrocarbons, and hexavalent chromium as assessed by the DOM-JEM (Table E4.4). All three categorical EC models (i.e., the main model and the two sensitivity models) showed the EC-exposure–lung cancer response among men, suggesting that the association is unlikely to be fully explained by confounding due to exposures to other occupational lung carcinogens.

Furthermore, because our JEM assigned EC exposures based on job titles, individual exposures may be misclassified in occupations with large exposure variability. This misclassification, however, was not likely to be differential by case status and introduced Berkson-like error that likely affected the precision, but not magnitude, of our risk estimates (32, 33). Exposure misclassification of jobs within the DEE- JEM may also have occurred because of the fact that our EC exposure data were limited and did not represent all jobs in all study regions. If present, this would introduce classical error in our work and bias the observed effect toward the null, meaning that the true effect of diesel exhaust exposure on lung cancer may be stronger than our observed results. However, the aforementioned shortcomings related to retrospective exposure assessment are almost inevitable because of our study design and size. We have provided details on all data sources, assessment procedures, and various sensitivity analyses in an effort to maximize transparency.

Another notable limitation of our study is the lower statistical power to assess risk in female workers (390 exposed cases) compared with males (7,843 exposed cases). Our results on female cancer risks may also have been affected by more exposure misclassification of women compared with men because the supporting EC exposure data were collected almost exclusively among male workers. Adenocarcinoma, for which we observed the weakest association with diesel exhaust exposure among the lung cancer subtypes, was also more common in women than in men. However, our results should not be interpreted as diesel exhaust having no effect on lung cancer risks in women. A sensitivity analysis among women with lung cancer subtypes other than adenocarcinoma showed increased OR point estimates for cancer for all cumulative EC exposure groups, albeit with larger uncertainties (Table E4.9).

In risk assessment for occupational carcinogen exposure, definitions for tolerable ELR range from 4 in 1,000 (0.4%) in the Netherlands and Germany to 1 in 1,000 (0.1%) in the United States (17, 34, 35). Of our three ELR estimates derived from different exposure limits, only the scenario with 1 mg/m$^3$ EC exposure and 0.04% ELR is below these levels. Another study using data from the U.S. trucking industry estimated that male workers exposed to 5 mg/m$^3$ EC would have a lung cancer ELR of 1–2% (5). A separate study calculated a lung cancer ELR of 0.17% for workers exposed to 1 mg/m$^3$ EC using data from three U.S. mining and trucking industry cohorts (7). Despite variations in the exact risk magnitude, estimates from different studies suggest that workplace EC levels should be at or near environmental background levels to reduce the lung cancer ELR for workers with lifetime exposure to diesel exhaust to tolerable levels, as defined by various national risk assessment agencies. Although multiple diesel engine emission control standards have been introduced in Europe since 2006 (17), these standards alone cannot be expected to reduce workplace EC exposure to environmental levels in the near future because they do not apply to the large number of existing diesel equipment that still is and will probably remain in use for many more years.

In summary, we observed a consistent exposure–response relationship between occupational diesel exhaust exposure and lung cancer in men in a large pooled analysis of case–control studies. Increased lung cancer risks were found in EC- exposed men who were never-smokers and smokers. Increased risks in men were also observed for all lung cancer subtypes included, with the strongest associations for squamous cell and small cell carcinomas and weaker for adenocarcinoma. The joint effects of EC exposure and smoking were superadditive on risks of overall lung cancer and all included subtypes. Our findings support efforts to further reduce workplace diesel exhaust exposure to protect workers against risks of lung cancer. n

Author disclosures are available with the text of this article at www.atsjournals.org.

References


1. Benbrahim-Tallaa L, Baan RA, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, *et al.*; 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.

2. Ilar A, Plato N, Lewne´ M, Pershagen G, Gustavsson P. Occupational exposure to diesel motor exhaust and risk of lung cancer by histological subtype: a population-based case-control study in Swedish men. *Eur J Epidemiol* 2017;32:711–719.

3. Olsson AC, Gustavsson P, Kromhout H, Peters S, Vermeulen R, Brü ske I, *et al*. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. *Am J Respir Crit Care Med* 2011;183:941–948.

4. Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, *et al*. The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust. *J Natl Cancer Inst* 2012;104:855–868.

5. Steenland K, Deddens J, Stayner L. Diesel exhaust and lung cancer in the trucking industry: exposure-response analyses and risk assessment. *Am J Ind Med* 1998;34:220–228.

6. Garshick E, Laden F, Hart JE, Davis ME, Eisen EA, Smith TJ. Lung cancer and elemental carbon exposure in trucking industry workers. *Environ Health Perspect* 2012;120:1301–1306.

7. Vermeulen R, Silverman DT, Garshick E, Vlaanderen J, Portengen L, Steenland K. Exposure-response estimates for diesel engine exhaust and lung cancer mortality based on data from three occupational cohorts. *Environ Health Perspect* 2014;122:172–177.

8. Parent M-E, Rousseau M-C, Boffetta P, Cohen A, Siemiatycki J.

9. Villeneuve PJ, Parent M-É , Sahni V, Johnson KC; 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.

10. Pintos J, Parent M-E, Richardson L, Siemiatycki J. Occupational exposure to diesel engine emissions and risk of lung cancer: evidence from two case-control studies in Montreal, Canada. *Occup Environ Med* 2012;69:787–792.

11. International Labour Organization. ISCO-International Standard Classification of Occupations: brief history [accessed 2018 Jul 20]. Available from: http://www.ilo.org/public/english/bureau/stat/isco/ intro2.htm.

12. Olsson AC, Vermeulen R, Schu¨ z J, Kromhout H, Pesch B, Peters S, *et al*. Exposure-response analyses of asbestos and lung cancer subtypes in a pooled analysis of case-control studies. *Epidemiology* 2017;28:288–299.

13. Ahrens W, Merletti F. A standard tool for the analysis of occupational lung cancer in epidemiologic studies. *Int J Occup Environ Health* 1998;4:236–240.

14. Mirabelli D, Chiusolo M, Calisti R, Massacesi S, Richiardi L, Nesti M, *et al*. [Database of occupations and industrial activities that involve the risk of pulmonary tumors] [in Italian]. *Epidemiol Prev* 2001;25: 215–221.

15. Dieselmotoremissionen (DME). Begrü ndung zu fü r Dieselmotoremissionen (DME) in TRGS 900 (Justification for diesel engine emissions (DME) in TRGS 900 - in German). [accessed 2019 May 24] Available from: https://www. baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/ Regelwerk/TRGS/pdf/900/900-dieselmotorenemissionen=Exposure to diesel and gasoline engine emissions and the risk of lung cancer. *Am J Epidemiol* 2007;165:53–62.dme-russpartikel-als-ec.pdf? v=5.

16. US National Institute for Occupational Safety and Health (NIOSH). Manual of Analytical Methods (NMAM) 4th Edition Third Supplement. Cincinnati, OH: CDC; 2003. DHHS (NIOSH) Publication No. 2003-154.

17. Health Council of the Netherlands. Diesel engine exhaust: health-based recommended occupational exposure limit. [accessed 2019 Jul 2]. Available from: https://www.gezondheidsraad.nl/binaries/

gezondheidsraad/documenten/adviezen/2019/03/13/ dieselmotoremissie/Diesel1Engine1Exhaust.pdf.
18. European Commission. Eurostat 2008 dataset on all causes and lung cancer mortality in European Union countries. [assessed 2012 Jun 1]. Available from: https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_cd_aro&lang=en.
19. Rothman K, Greenland S. Modern Epidemiology. Philadelphia, PA: Lippincott - Raven; 1998.
20. Knol MJ, VanderWeele TJ, Groenwold RHH, Klungel OH, Rovers MM, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. *Eur J Epidemiol* 2011;26:433–438.
21. Attfield MD, Schleiff PL, Lubin JH, Blair A, Stewart PA, Vermeulen R, *et al*. The Diesel Exhaust in Miners study: a cohort mortality study with emphasis on lung cancer. *J Natl Cancer Inst* 2012;104: 869–883.
22. 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.
23. Sa¨ verin R, Bra¨ unlich A, Dahmann D, Enderlein G, Heuchert G. Diesel exhaust and lung cancer mortality in potash mining. *Am J Ind Med* 1999;36:415–422.
24. Vermeulen R, Portengen L. Is diesel equipment in the workplace safe or not? *Occup Environ Med* 2016;73:846–848.
25. Guo J, Kauppinen T, Kyyrö nen P, Lindbohm M-L, Heikkilä P, Pukkala E.
26. 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 Causes Control* 2001;12:365–374.
27. VanderWeele TJ, Knol MJ. A tutorial on interaction. *Epidemiol Methods* 2014;3:33–72.
28. Emmelin A, Nyströ m L, Wall S. Diesel exhaust exposure and smoking: a case-referent study of lung cancer among Swedish dock workers. *Epidemiology* 1993;4:237–244.
29. Ge CB, Friesen MC, Kromhout H, Peters S, Rothman N, Lan Q, *et al*. Use and reliability of exposure assessment methods in occupational case-control studies in the general population: past, present, and future. *Ann Work Expo Health* 2018;62:1047–1063.
30. Teschke K, Olshan AF, Daniels JL, De Roos AJ, Parks CG, Schulz M, *et al*. Occupational exposure assessment in case-control studies: opportunities for improvement. *Occup Environ Med* 2002;59: 575–593. [Discussion p. 594.]
31. Plato N, Lewne´ M, Gustavsson P. A historical job-exposure matrix for occupational exposure to diesel exhaust using elemental carbon as an indicator of exposure. *Arch Environ Occup Health* 2019;0:1–12.
32. Armstrong BG. The effects of measurement errors on relative risk regressions. *Am J Epidemiol* 1990;132:1176–1184.
33. Heid IM, Ku¨ chenhoff H, Miles J, Kreienbrock L, Wichmann HE. Two dimensions of measurement error: classical and Berkson error in residential radon exposure assessment. *J Expo Anal Environ Epidemiol* 2004;14:365–377.
34. AGS. TRGS 910 Risikobezogenes Maßnahmenkonzept fu¨ r Ta¨ tigkeiten mit krebserzeugenden Gefahrstoffen (Technical Rules for Hazardous Substances 910: risk-based action plan for activities with carcinogenic hazardous substances - in German). [accessed 2019 Jul 2]. Available from: https://www.baua.de/DE/Angebote/ Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/TRGS-
35. Rodricks JV, Brett SM, Wrenn GC. Significant risk decisions in federal regulatory agencies. *Regul Toxicol Pharmacol* 1987;7:307–320.

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