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On the Dose-Response Relationship between Occupational Exposure to Diesel Engine Emissions and Lung Cancer Risk—A Critical Appraisal of the Current Stage of Epidemiological Research

Matthias Möhner †

Federal Institute for Occupational Safety and Health, D-10317 Berlin, Germany; Matthias.Moehner@web.de
† Retired.

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Abstract: The Diesel Exhaust in Miners Study (DEMS) played a decisive role in the classification of diesel engine emissions as a Group 1 carcinogen by the International Agency for Research on Cancer. However, the statistical analysis of this extensive cohort study and the interpretation of the results have been widely criticized. Recently, a comprehensive systematic review was published whose meta-analysis revealed a statistically significant positive linear dose-response relationship. The results of the case-control approach from the DEMS contributed significantly to this result. However, the contradictory results of the mortality analysis for the entire cohort were not mentioned. The method for estimating the linear dose-response relationship in the studies included in the aforementioned systematic review must also be scrutinized from a methodological point of view. Meanwhile, the follow-up of the DEMS-cohort has been extended by 18 years, which has significantly strengthened the database for the analysis. The results of this important data material and its effects on the meta-analysis are discussed. Ultimately, the meta-analysis was reanalyzed, corrected for the shortcomings identified.

Keywords: meta-analysis; diesel engine emissions; lung cancer; dose-response relationship

1. Introduction

In 2012, the International Agency for Research on Cancer (IARC) classified diesel engine emissions (DEE) as a Group 1 carcinogen [1]. The Diesel Exhaust in Miners Study (DEMS) played a key role in this categorization [2,3]. However, the statistical analysis of this extensive cohort study and the interpretation of the results have been widely criticized [4–10]. Recently, a comprehensive systematic review was published in which a total of 15 studies were identified that met the authors' quality criteria and whose meta-analysis revealed a statistically significant positive linear dose-response relationship [11]. In this analysis, the DEMS was the only study to be recognized as having an overall low risk of bias. However, the critical comments on this study were not considered. Even the large discrepancy between the results of the mortality analysis of the entire cohort and those of the nested case-control study was not mentioned.

The method used to estimate the linear dose-response relationship in the studies included in the systematic review must also be examined from a methodological perspective. Furthermore, several peculiarities of studies included in the systematic review have also not been considered. A review of all studies included in the meta-analysis, primarily from a methodological perspective, therefore seemed necessary. Moreover, an update of the DEMS has now been published, which has significantly strengthened the database by extending the follow-up by 18 years [12,13]. The results of this important data material and its effects on the meta-analysis are discussed below.

2. Materials and Methods

2.1. Methods for Dealing with the DEMS

The DEMS cohort comprises 12,315 workers in eight non-metal mines who had worked in one of the mines for at least one year after the introduction of diesel technology. The DEE exposure differed significantly between the surface and underground workplaces [2]. Thus, this study covers a very broad exposure spectrum, both in terms of exposure intensity and cumulative exposure.

The a priori specified analyses of the entire cohort could not demonstrate a dose-response relationship between DEE and lung cancer mortality [2]. In contrast, the embedded case-control study, in which smoking was adjusted for, showed an effect [3]. However, smoking was not adjusted for in the usual way. The authors observed an interaction between cigarette smoking and location of employment, after adjustment for cumulative respirable elemental carbon (REC) lagged 15 years ($p_{interaction} = 0.082$). Based on this, they included a variable that combined cigarette smoking status and smoking intensity with location of employment in their final models instead of smoking. But the cumulative DEE exposure is highly correlated with membership of one of the two sub-cohorts. Therefore, it cannot be ruled out that adjusting for this variable distorts the risk estimators, which could explain the divergence between the results of the cohort and case-control approach.

Comparing the results from the initial observation period with those from the subsequent 18-year period may reveal differences between the two sub-cohorts with regard to smoking, for example, and thus contribute to validating and appraising the estimated dose-response relationship.

2.2. Methods for Estimating the Slope in a Dose-Response-Relationship

A total of 65 publications pertaining to 34 studies were identified in the systematic review [11] in which information on the subjects' occupational DEE exposure was available or could be estimated via a job-exposure-matrix (JEM). The final dose-response meta-analysis is based on 15 studies, which met the authors' quality criteria. For most of these studies, only category-specific risk estimates were published. To estimate the slopes for each of these studies, the authors used fixed-effects linear models, that account for the correlation between category-specific risk estimates within a single study [14–16].

These models were also used for the present recalculation of the slopes. However, to be able to recognize a difference in the study-specific risk estimators not related to DEE exposure, which could be induced, for example, by a selection bias in a case-control study, a second model variant was considered, in which an intercept was included in addition to the slope. Model fit for the single studies was determined using the Akaike information criterion [17] and the slope from the better model (either with or without intercept) was used to recalculate the meta-analysis.

In those studies where only occupational history data were available for the subjects, exposure was estimated using an external JEM [11]. As it cannot be ruled out that the use of an external JEM may have led to bias in the analysis, a final check was carried out to determine whether the risk estimators determined for the single studies based on the linear models are generally compatible with the published results of the original studies. In the case of contradictory results, the corresponding study was not included in the reanalysis. Ultimately, the meta-analysis was reanalyzed, corrected for the shortcomings identified.

All calculations were performed with STATA 17.0 [18].

3. Results

3.1. Findings for the DEMS

Information on smoking was only available for workers included in the case-control approach. This is why smoking could not be taken into account in the cohort approach. However, information on smoking among the control group may provide insight into potential differences between the two sub-cohorts of underground and surface workers. As shown in Table 1, underground workers smoke significantly more (Pearson's χ^2-Test yields $p < 0.05$). Therefore, the ratio of lung cancer SMR between ever-underground and surface-only workers [12], which is 1.03 (95% CI: 0.84, 1.27), does not underestimate the DEE-related lung cancer risk due to a lack of adjustment for smoking (calculated according [19], p. 95).

Table 1. Smoking intensity among controls by worker location in DEMS II *.

Smoking Intensity (Packs per Day)	Surface-Only *n* (%)	Ever-Underground *n* (%)
Never smoker	100 (32.5)	132 (24.6)
Light smoker, (<1) §	87 (28.2)	150 (28.0)
Heavy smoker, (≥1)	121 (39.3)	254 (47.4)

* Data from Table S1 [13], § includes unknown smoking status.

No information is available on the age structure of the cohort. However, the quotient of the number of expected deaths and the person-years provides the average expected annual mortality rate in an age-matched cohort from the reference population. For surface workers, this value is significantly higher than for underground workers (Table 2), i.e., they are significantly older (Pearson's χ^2-Test yields $p < 0.01$).

Table 2. Person years and mean expected annual death rate by worker location in DEMS II *.

Work Location	Surface Only	Ever Underground
Person years (PY)	139,503	282,840
Number of deaths	1628	3259
Expected deaths (EXP)	1713.7	3074.5
EXP/1000 PY	12.28	10.87

* Data from Table 1 [12] and own calculations.

Discrepancies in the age structure of sub-cohorts have the capacity to influence not only the SMR comparison over consecutive time intervals (see Table 3), but also the outcomes of an age-adjusted case-control study, particularly in instances where the matching ratio is not constant. Although the ratio of lung cancer SMR between ever-underground and surface-only workers increases between the two study periods [0.91 (95% CI: 0.68, 1.22) resp. 1.19 (95% CI: 0.88, 1.63)], the difference is not statistically significant ($p > 0.2$).

Table 3. Observed numbers of deaths and standardized mortality ratios (SMRs) for selected causes of death by worker location and time in the DEMS *.

Cause of Death	Location	1960–1997		1998–2015	
		Observed	SMR (95% CI)	Observed	SMR (95% CI)
All causes	Surface-only	797	0.90 (0.84, 0.96)	831	1.00 (0.94, 1.07)
All causes	Ever-underground	1388	0.95 (0.90, 1.01)	1871	1.16 (1.11, 1.21)
Lung cancer	Surface-only	81	1.33 (1.06, 1.66)	62	1.10 (0.84, 1.41)
Lung cancer	Ever-underground	122	1.21 (1.01, 1.45)	144	1.31 (1.10, 1.54)

* Data from Table 3 [2] and own calculations based on Table 1 [12].

A comparison of the risk estimators from the case-control approach between the original period and the 18 subsequent years is not available. However, a comparison of the results between DEMS and DEMS II shows that, with the addition of the matched sets from the period 1998–2015, the risk estimators in all exposure categories above 160 µg/m^3-years were considerably lower than in the original analysis (Table 4). Given that 198 matched sets with 666 controls were included in the initial analysis and only 178 one-to-one matched sets were added due to the extended period, it can be concluded that the power of the 178 matched sets allone is considerably lower than that of the initial analysis. Such a substantial reduction in risk estimators from the initial to the extended analysis therefore indicates that a separate analysis of the 178 additional matched sets would not have revealed any increase in risk.

The mean exposure intensity for ever-underground and surface-only workers was determined to be 128.2 µg/m^3 or, respectively, 1.7 µg/m^3 [2]. The mean time spent working underground was reported as eight years, although the mean cumulative exposure or exposure time for the two sub-cohorts was not reported in the primary publication [2]. However, based on this information, it can be assumed that there is a difference of approximately 1000 µg/m^3-years between the two sub-cohorts.

Table 4. Odds ratios (OR) and 95% confidence intervals (95% CI) for cumulative respirable elemental carbon (REC) in DEMS and DEMS II *.

Cumulative REC	1960–1997 (DEMS)		1960–2015 (DEMS II)	
15-Year Lagged, µg/m³-y	OR	95% CI	OR	95% CI
0 to <20	1.00		1.00	
20 to <40	0.49	0.20, 1.20	0.68	0.34, 1.36
40 to <80	1.16	0.40, 3.39	1.59	0.73, 3.45
80 to <160	1.40	0.58, 3.38	1.20	0.57, 2.54
160 to <320	2.13	0.91, 5.02	1.34	0.66, 2.73
320 to <640	1.71	0.77, 3.79	1.48	0.76, 2.90
640 to <1280	4.30	1.88, 9.84	3.28	1.63, 6.59
1280 to <2560	2.13	0.76, 6.00	1.62	0.71, 3.71
≥2560	3.14	0.61, 16.09	1.40	0.61, 3.22

* Data taken from Table S2 [2] and Table S3 [13].

Given the serious differences in exposure between the two sub-cohorts, the most obvious and simplest analytical approach under the case-control design would be one in which membership of the sub-cohort acts as a binary exposure variable. Regardless of whether there is a linear, log-linear, or other monotonic dose-response relationship between DEE and lung cancer risk, this analytical approach should yield a significantly elevated risk estimator if a true causal relationship exists. Of the 376 lung cancer cases in the expanded case-control study, 124 had only worked on surface [13]. Among the controls, this applied to 308 of 844 workers. Without any adjustment and based solely on unconditional regression, this results in an OR = 1.17 (95% CI: 0.90, 1.52). If the analysis is reduced to only the 178 matched sets from the added follow-up, the risk estimator OR = 1.11 (95% CI: 0.69, 1.81) results.

3.2. Results of the Reanalysis for the Meta-Analysis

The reanalysis included 14 studies of the original 15 studies [12,20–32]. Risk estimates assuming a linear dose-response relationship were available for two of the original studies [24,32]. These estimates are based on the complete data set, which is why a loop via category-specific risk estimators is not necessary. For the remaining studies, estimates were calculated based on the available category-specific data. For six studies, the inclusion of an intercept in the linear model led to a better model fit (Table 5).

Table 5. Model selection for fixed-effect models accounting for the correlation between estimates.

Study	Model without Intercept			Model with Intercept				
First Author, Year	Slope	95%-CI	AIC §	Slope	95% CI	Intercept	95% CI	AIC §
Garshick, 2012 [22]	1.005	0.987, 1.024	**−3.99**	1.004	0.983, 1.025	1.041	0.783, 1.385	−2.07
Petersen, 2010 [28]	0.995	0.972, 1.019	**0.32**	1.007	0.937, 1.081	0.834	0.287, 2.426	2.21
Garshick, 2006 [23]	1.063	1.039, 1.087	2.26	0.982	0.940, 1.026	1.273	1.134, 1.429	**−12.55**
Soll-Johanning, 2003 [31]	0.974	0.952, 0.996	6.67	0.970	0.947, 0.993	2.745	0.849, 8.872	**5.82**
Menvielle, 2003 (women) [33]	1.048	0.995, 1.104	2.67					
Menvielle, 2003 (men) [33]	1.024	1.006, 1.041	**16.08**	1.031	1.005, 1.057	0.845	0.525, 1.361	17.60
Pezzotto, 1999 [29]	1.028	1.009, 1.048	**3.44**	1.021	0.960, 1.086	1.177	0.315, 4.403	5.38
Hansen, 1998 [25]	1.041	1.021, 1.062	5.92	1.020	0.996, 1.045	1.231	1.065, 1.424	**0.04**
De Stefani, 1996 [21]	1.000	0.986, 1.015	**11.61**	0.999	0.979, 1.020	1.025	0.728, 1.444	13.59
Hayes, 1989 [26]	1.012	1.004, 1.021	12.50	1.005	0.995, 1.015	1.469	1.136, 1.899	**5.90**
Rafnsson, 1991 [30]	1.147	1.014, 1.297	12.16	0.980	0.820, 1.171	2.517	1.182, 5.358	**8.42**
Paradis, 1989 [27]	0.995	0.985, 1.005	**−1.40**	0.989	0.962, 1.018	1.149	0.609, 2.169	0.42
Damber, 1987 [20]	0.983	0.967, 1.000	8.29	1.014	0.983, 1.047	0.592	0.378, 0.927	**5.02**

§ AIC—Akaike information criteria. The AIC of the better model is highlighted in bold.

The comparison of the risk estimates with the original publications revealed discrepancies in one study [33]. The application of the JEM on the study in New Caledonia led to a significantly increased risk of lung cancer in DEE-exposed men. In contrast, no increased risk was reported in the original study, which was based on interviews with the subjects and in which DEE exposure was explicitly asked about [33]. Even for the highest exposure category, only odds ratio OR = 0.7 was reported. It is notable that using the JEM instead of the subjects' information significantly increased the proportion of subjects classified as exposed, by 45% among cases but only by 23% among controls. The authors of the original study also point to a high level of environmental pollution from asbestos, particularly in the agricultural sector. Hence, this study was excluded from recalculation of the meta-analysis.

The meta-analysis also included a study from the north of Sweden [20]. In this study, a particularly high risk of lung cancer was reported for iron ore miners. The authors of the primary study consider as main reason for this

the high radon exposure that prevailed in the poorly ventilated shafts [20]. This occupational group was therefore not considered when estimating the slope. However, the estimate based on the remaining occupational groups was included in the recalculation of the meta-analysis

The meta-analysis used the results of the DEMS case-control approach [11,34]. For the reasons mentioned above, the results of the cohort approach were used for the reanalysis [12]. The available data resulted in a relative risk of RR = 1.0328 (95% CI: 0.8397, 1.2746) (cf. [19], p. 95). As already explained, it can be assumed that the cumulative exposure of ever-underground workers was approximately 1000 µg/m^3 higher than that of surface-only workers. In relation to the exposure unit 10 µg/m^3-y, this results in a relative risk of RR = 1.0003 [95% CI: 0.9983, 1.0024] for the DEMS.

The final recalculation of the meta-analysis revealed a weak increase in the risk of lung cancer (RR per 10 µg/m^3-y: 1.0023 [95% CI: 1.0002, 1.0044]) (Figure 1). Although the results differ significantly between case-control and cohort studies, they are homogeneous within these subgroups.

As a type of sensitivity analysis, the estimate for the slope parameter calculated from the model with intercept was used for all studies. However, the results are virtually identical to those shown in Figure 1 (RR per 10 µg/m^3-y: 1.0023 [95% CI: 1.0003, 1.0043], data not shown).

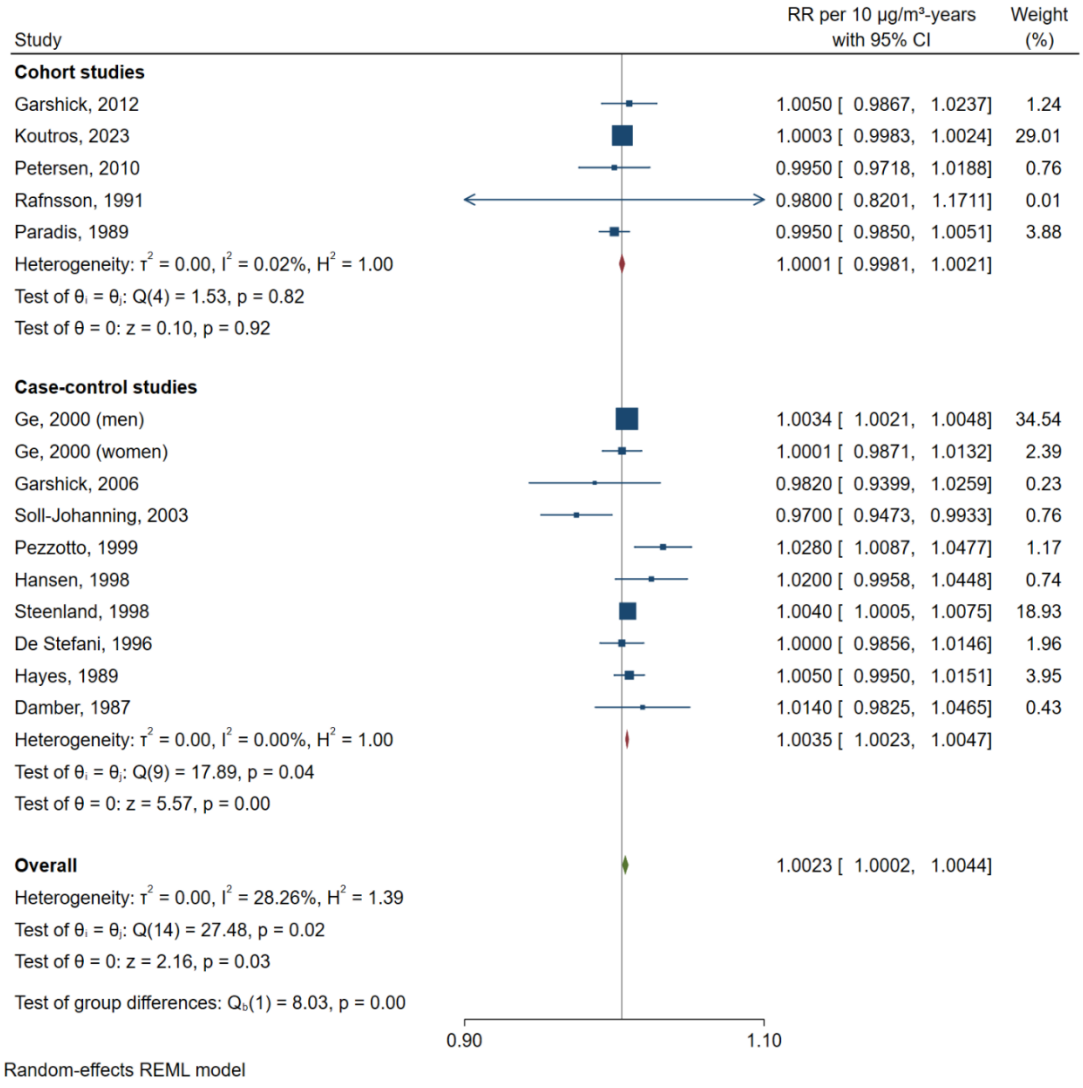

Figure 1. Forest plot for studies used for recalculation [12,20–32].

4. Discussion

The disparate conclusions pertaining to dose-response relationship between DEE and lung cancer risk from the DEMS have a substantial impact on the divergent results of the meta-analyses. The pivotal point in this regard is the adjustment for smoking in the case-control approach of the DEMS using a categorical variable that combines smoking status with location worked, the latter of which is highly correlated with exposure.

In the initially published results of the case-control study, smoking was defined as a variable comprising eight categories (smoking status, smoking intensity) [3]. In the later analysis, the results of which were included in the meta-analysis, the combination of smoking status, smoking intensity (packs/day), and smoking duration resulted in as many as 32 categories [11,34]. Due to the additional combination with location worked, 15 or even 63 parameters had to be estimated in the final models for the adjustment of smoking.

The well-known statistician George Box coined the now legendary phrase "All models are wrong but some are useful" and advocates for parsimonious models [35]. The objective of parsimony can be achieved by minimizing the sum of model bias and estimation error. The Akaike criterion is well-tried in model selection procedures for this purpose [17]. In order to verify the suitability of the selected adjustment variables for smoking in the extended DEMS, it is necessary to use appropriate statistical methods such as cross-validation. Using the 178 matching pairs from the most recent study period, it could be verified whether there is also an interaction between cigarette consumption and location worked after adjustment for DEE. Since the DEMS covers data from eight mining facilities and the facility was taken into account as a matching factor, the leave-one-cluster-out cross validation taking the facilities as clusters may be even more suitable for comparing the performance of different adjustment variables for smoking (methods described for example in [36]).

In occupational epidemiology, the use of a metric variable for cumulative smoking of cigarettes (packyears), usually in logarithmic form, together with a categorical variable describing the time since quitting smoking, has proven effective for adjusting for smoking in studies on lung cancer risk. For example, in a large, pooled analysis of 14 case-control studies comprising 16,901 cases and 20,965 controls, only six parameters were used for smoking adjustment [24]. Compared to the models used in DEMS, this is a truly parsimonious model.

It is also important to critically examine whether the smoking variable used in the DEMS case-control approach is at all suitable for reflecting possible differences in the effects of smoking between the two sub-cohorts of ever-underground and surface-only workers. It is plausible that smokers who work in workplaces where smoking is prohibited will adjust their smoking behavior accordingly. Some will reduce their tobacco consumption, others will spread their usual daily tobacco consumption over their non-working hours, and still others will try to smoke secretly during breaks. The change in smoking behavior during underground employment may have led to biased information about smoking, as this information often comes from relatives who can only observe workers' smoking habits during leisure time.

As already explained in an earlier comment on the DEMS, it is possible that the attenuated smoking effect at underground workplaces is the result of a negative residual confounding effect of smoking [10].

If detailed smoking data is available, a corrected estimate of the corresponding packyears could be calculated. However, the DEMS case-control approach assumes that the lung cancer risk associated with smoking is permanently reduced when underground work begins, i.e., not only until the end of underground work, but until the end of the follow-up. The latter seems implausible. To the author's knowledge, there have been no recorded observations of this kind in other mining sectors.

In summary, it is important to note that the adjustment for smoking using the combination variable of smoking intensity and location worked is not adequately justified and validated. Therefore, the results from the cohort approach are considered more reliable, and they do not confirm an increased risk of lung cancer from exposure to DEE.

In addition to the interpretation of the DEMS results, the consideration of possible selection effects and confounding in the modeling of the risk increases in the other studies also contributed to the fact that the result of the reanalysis differs significantly from that of the original meta-analysis.

For six studies, the dose-response parameter based on an intercept-based regression model resulted in a better model fit than the parameter calculated without an intercept (Table 5, see Figure 2 as an example). Among these six studies, there was only one cohort study, investigating the SMR of truck drivers with respect to duration of employment [30]. The highest lung cancer mortality was determined for the lowest DEE exposure category in this study—a clear indication of a bias [30]. Truck drivers smoke significantly more than the general population [37] and also differ in terms of socio-economic parameters such as highest level of education. The lack of adjustment for these factors is likely to have caused this bias.

Among the five case-control studies, one study stands out with an estimate for the intercept significantly below one [20]. The underlying cause of this phenomenon is likely to be attributed to the high exposure of the study population to established lung carcinogens, including radon progeny, arsenic, and, notably, asbestos.

One study was excluded from the reanalysis, as their results published by the original study authors [33] differed strongly from the dose-response parameter derived by fixed-effects linear models based on DEE-JEM [11]. The original study reported an OR = 0.8 (95% CI: 0.5, 1.2) for subjects ever exposed to DEE and for the highest decile of exposure, the OR was reported as 0.7 [33].

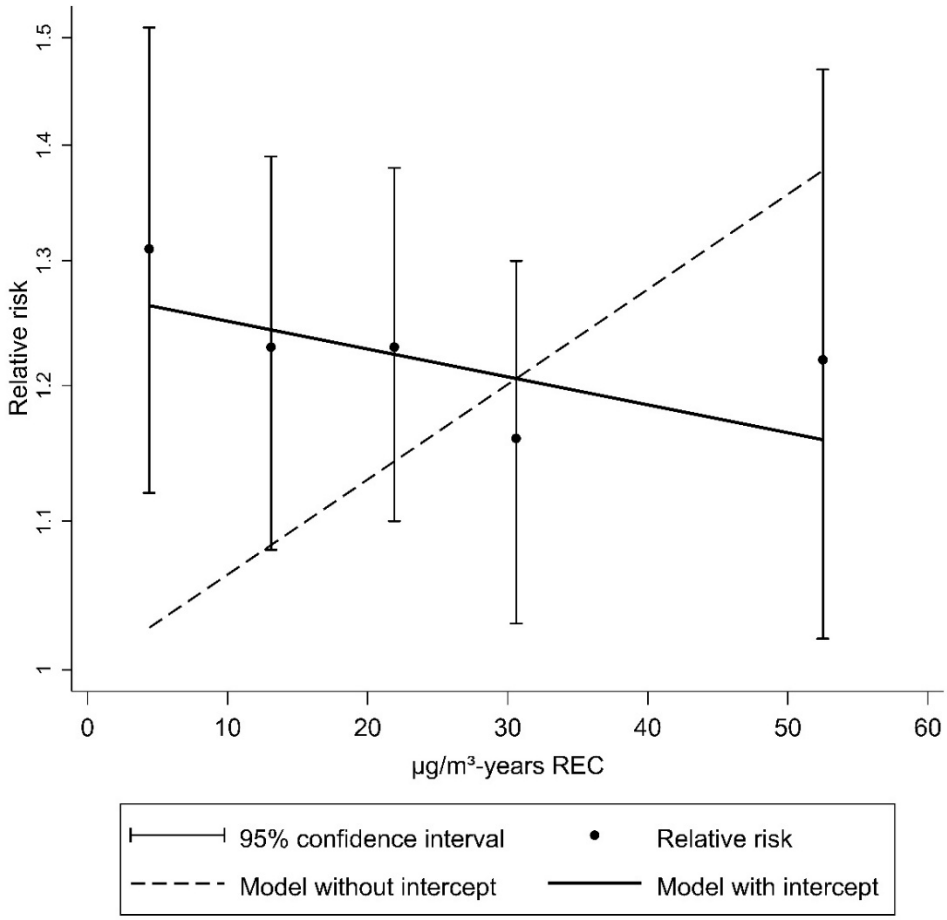

Figure 2. Model comparison based on data from [23].

In addition, another cohort study from underground potash mining should be mentioned here, in which similarly high exposures to DEE occurred as in the DEMS [38–40]. This study was not included in the original meta-analysis because of high mean cumulative exposure among controls of the nested case-control study [11]. Adjusted for smoking and previous occupation, the risk increase was RR = 1.16 (95% CI: 0.85, 1.58) per 1 mg/m^3-years, based on the full cohort data set [38]. Based on 10 µg/m^3-years, this corresponds to a relative risk of RR = 1.0015 (95% CI: 0.9984, 1.0046) and is thus close to the result of the DEMS cohort approach [12]. Even from the results of the case-control approach for the extended DEMS, the linear model for the dose-response relationship yields RR = 1.0016 (95% CI: 0.9996, 1.0035) (Table S3 [13]).

The recalculation of the meta-analysis also shows that case-control studies lead to a slightly higher risk estimate than the cohort studies. Selection bias and confounding due to other occupational exposures are likely to be responsible for this. This problem will be discussed based on the two most comprehensive of these studies, the SYNERGY study—a pooled analysis of 14 hospital- and population-based lung cancer case–control studies [24]—and the case-control study in the Teamsters Union [32].

The sensitivity analyses for the extensive SYNERGY study [24] show this very clearly. Two of the pooled studies were characterized by significantly higher risk estimates than the remaining studies ([24], Table E4.5). One of these, PARIS, restricted the recruitment of cases and controls to regular smokers [41]. The controls are therefore no longer representative of the base population when studies are pooled. The second study, AUT-Munich, is a secondary analysis of a large data set that was primarily gathered to investigate the effect of indoor radon exposure on the risk of lung cancer [42]. As part of the exposure assessment, extensive data was gathered, including radon measurements in the subject's current home and in previous homes. However, these data are unlikely to allow any conclusions about the radon exposure of a long-standing long-haul truck driver who has had to spend most nights away from home during his working life. The response rates among long-haul truck drivers may have been considerably lower and, hence, caused a selection bias. Subsequent calculations based on census data have confirmed this suspicion [39].

Restricting the analysis to the blue-collar workers also led to a significant reduction in the estimator for lung cancer risk ([24], Table E4.2). As a method to reduce the selection bias in population-based case-control studies, access to the controls via general practitioners was recommended [43]. This method was used in two of the studies included in the SYNERGY project (EAGLE, INCO-UK) [44,45]. The estimates for the odds ratios in both studies did not exceed one [41].

No increase in risk was observed for women in the SYNERGY study. It can be assumed that, in contrast to their male colleagues, only a very small proportion of women exposed to DEE work as long-haul truck drivers and therefore this kind of selection bias doesn't play a role here.

Confounding by other occupational lung carcinogens is also likely to play a role in the SYNERGY study ([24], Table E4.4). However, bias due to smoking is less likely in this study due to the detailed history of smoking.

In contrast to the SYNERGY study, residual bias due to smoking must be assumed in the case-control study in the Teamsters Union [32]. The odds ratios reported for current smokers [46] are two to three times lower than in the SYNERGY study [47]. The rough smoking categories, which are hardly comparable between age groups, may have led to an underestimation of the smoking-related risk and thus to an overestimation of the DEE-related lung cancer risk.

5. Conclusions

Overall, it can be concluded that there is no clear evidence from the recalculated meta-analysis for an increase in lung cancer risk with increasing DEE exposure. This result is compatible with the results of animal studies. Lung tumors were only identified at exposures of 2.5 mg/m^3 upwards [48]. In the studies of underground mining the exposure intensity was about 10 times lower, and again 10 times lower in surface mining and other surface jobs.

A further reduction of the current threshold levels for DEE exposure at the workplace is therefore not warranted.

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Institutional Review Board Statement

This research is based exclusively on previously published results and therefore does not require ethical review and approval.

Informed Consent Statement

Not applicable.

Data Availability Statement

All data used can be found in the publications cited.

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Conflicts of Interest

The author declares no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the author used DeepL to improve the language and correct typos and grammatical errors. After using this tool, the author reviewed and edited the content as needed and is fully responsible for the article.

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