Draft for public review

Gezondheidsraad

Diesel Engine Exhaust

Health-based recommended occupational exposure limit

Dutch Expert Committee on Occupational Safety (DECOS)
a committee of the Health Council of the Netherlands

Your comments before: February 5, 2018

Preferentially bij e-mail
draftOSH@gr.nl
Attn: Ms. J.M. Rijnkels

The Health Council
PO Box 16052
2500 BB The Hague
The Netherlands

All comments received, and the replies by the DECOS, will be publicly available on the website www.gezondheidsraad.nl from the moment of publication of the final advisory report.

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Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad een risicoschatting opgesteld voor beroepsmatige blootstelling aan uitstoot (emissie) van dieselmotoren. De Gezondheidsraad heeft blootstellingniveaus afgeleid die overeenkomen met vooraf vastgestelde risiconiveaus voor het overlijden aan longkanker bij beroepsmatige blootstelling aan dieselmotoremissie. Het blootstellingniveau dat overeenkomt met het streefrisiconiveau is 0,011 microgram (µg) inhaleerbare elementaire koolstofdeeltjes per kubieke meter (m^3) lucht. Het blootstellingniveau dat overeenkomt met het verbodsrisiconiveau is 1,03 µg /m^3. Die blootstellingniveaus zijn veel lager dan de concentraties die op werkplekken worden gemeten. Door uitlaatgassen van dieselmotoren in het verkeer variëren de concentraties elementaire koolstofdeeltjes in Nederlandse steden tussen de 0,4 en 2 µg per kubieke meter – dus boven het streefrisiconiveau, en in sommige gevallen zelfs boven het verbodsrisiconiveau. Dit betekent dat de commissie aanbeveelt dat werknemers niet hoger blootgesteld mogen worden aan dieselmotoremissie dan het achtergrondniveau.

Dit advies is tot stand gekomen in de commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) - een vaste commissie van de Gezondheidsraad.

De Gezondheidsraad heeft een vaste rol bij de bescherming van werknemers tegen mogelijke schadelijke effecten van stoffen waar zij tijdens hun werk mee in aanraking kunnen komen. Meer informatie hierover staat op www.gezondheidsraad.nl.

Dieselmotoremissie: breed scala aan gezondheidrisico's voor een breed scala aan werknemers

Gezondheidsrisico's

Dieselmotoremissie bestaat uit een mengsel van verschillende gassen en deeltjes die geproduceerd worden tijdens de verbranding van diesel in de motor. De emissie bevat stoffen die bij inademing schadelijk zijn voor de gezondheid. Mogelijke gezondheidseffecten zijn: ontstekingsreacties in de longen, aandoeningen van hart en bloedvaten, allergische aandoeningen, toename van astmatische klachten, en verschillende typen kanker - met name longkanker en blaaskanker.

Blootstelling in de algemene populatie en op de werkvloer

Dieselmotoren worden wereldwijd gebruikt voor transport (de aandrijving van onder meer vrachtwagens, treinen, schepen, autobussen, tractoren en auto's) en stroomvoorziening (compressoren, pompen en kleine generatoren). De algemene bevolking wordt blootgesteld door uitlaatgassen van dieselmotoren in het verkeer. Werknemers kunnen daar bovenop extra blootgesteld worden in de werkomgeving. Voorbeelden van beroepen met extra blootstelling zijn: bouwvakkers, automonteurs en chauffeurs. Daarnaast komt extra blootstelling aan dieselemissie ook voor in industrieën waar motoren en apparaten met een dieselaandrijving worden gebruikt, zoals in de bouw, de scheepvaart, landbouw, bosbouw, afvalverwerking en spoorwegen.

Europese emissienormen voor nieuwe dieselmotoren

De afgelopen twee decennia zijn de emissienormen voor dieselmotoren in Europa strenger geworden. Deze normen gelden voor alle nieuw geproduceerde dieselmotoren in voertuigen en voor motoren en apparaten met een dieselaandrijving. Door nieuwe technologieën is de totale massa van deeltjes in dieselemissie met 90% afgenomen. Ook de samenstelling van de emissie is veranderd, er zitten in verhouding minder elementaire koolstofdeeltjes in. Emissie van nieuwe dieselmotoren bevat dus minder schadelijke deeltjes, maar dat geldt niet voor de oude dieselmotoren. Doordat dieselmotoren in de werkomgeving lang meegaan, verwacht de commissie dat veel mensen op de werkvloer nog worden blootgesteld aan dieselemissie door motoren van de oude generatie.

Longkanker uitgangspunt voor het afleiden van risicogetallen

Dieselmotoremissie kan leiden tot een breed scala aan gezondheidseffecten. De commissie heeft ervoor gekozen de berekening van de blootstellingniveaus te baseren op gegevens over kanker, vanwege de ernst van die ziekte. Voor longkanker zijn drie grote cohortonderzoeken beschikbaar met gegevens van goede kwaliteit over blootstelling aan dieselmotoremissie en risico op longkankersterfte. Voor blaaskanker zijn dergelijke onderzoeken niet beschikbaar. De commissie is daarom uitgegaan van de gegevens over longkanker.

Dieselmotoremissie bevat kankerverwekkende stoffen die het genetisch materiaal (DNA) in cellen kan beschadigen. Dit werkingsmechanisme wordt een stochastisch genotoxisch werkingsmechanisme genoemd. Voor dit type stoffen is geen niveau aan te geven waaronder geen kankervorming meer optreedt en verondersteld wordt dat er bij elk blootstellingniveau een bepaalde kans bestaat op het ontstaan van kanker. In dit geval is de aanpak gericht op het beperken van risico. De minister van SZW heeft vooraf twee risiconiveaus vastgesteld: een streefrisiconiveau en een

verbodsrisiconiveau. Deze komen respectievelijk overeen met 4 extra gevallen aan kanker door beroepsmatige blootstelling gedurende 40 jaar, per 100.000 en per 1.000 algemene gevallen in de bevolking. Ter illustratie, als van elke 100.000 mannen die in Nederland overlijden er 12.000 overlijden door longkanker, dan komt het streefrisiconiveau in absolute zin overeen met 4 plus 12.000 is 12.004 gevallen per 100.000 algemene sterfgevallen. De commissie berekent welke blootstellingniveaus overeenkomen met de vastgestelde risiconiveaus; deze blootstellingniveaus worden risicogetallen genoemd.

Meta-analyse van drie cohortonderzoeken

Voor het meten van emissie van dieselmotoren is de beste blootstellingmaat inhaleerbare elementaire koolstofdeeltjes. Elementair koolstof is een specifieke en gevoelige indicator voor dieselmotoremissie. Het is geschikt als merkstof voor dieselmotoremissie omdat het goed te meten is en een nauwkeurige weergave geeft van de concentratie deeltjes in de emissie. Daarnaast zijn dieselmotoren op de meeste werkplekken de enige bron van emissie van elementair koolstof.

De commissie berekent risicogetallen bij voorkeur op basis van epidemiologische onderzoeken en heeft hiervoor drie grote cohortonderzoeken geschikt bevonden. Het gaat om een onderzoek onder mijnwerkers en twee onder werknemers van transportbedrijven. In alle drie onderzoeken is gekeken naar de relatie tussen longkankersterfte en kwantitatieve blootstelling aan emissie van dieselmotoren, uitgedrukt in inhaleerbare elementaire koolstofdeeltjes/m^3.

De commissie heeft de drie cohortonderzoeken samengevoegd op basis van samengevatte gegevens. Door het samenvoegen van verschillende onderzoeken (een meta-analyse) kan een meer betrouwbare uitkomst worden verkregen. Op basis van de meta-analyse heeft de commissie de volgende risicogetallen afgeleid voor dieselmotoremissie:

- 0,011 µg inhaleerbare elementaire koolstofdeeltjes/m^3, dat overeenkomt met een extra kans van 4 gevallen van overlijden aan longkanker bij beroepsmatige blootstelling gedurende 40 jaar aan emissie van dieselmotoren, per 100.000 sterfgevallen in de algemene bevolking (streefrisiconiveau).
- 1,03 µg inhaleerbare elementaire koolstofdeeltjes/m^3, dat overeenkomt met een extra kans van 4 gevallen van overlijden aan longkanker bij beroepsmatige blootstelling gedurende 40 jaar aan emissie van dieselmotoren, per 1.000 sterfgevallen in de algemene bevolking (verbodsrisiconiveau).

Concentraties elementaire koolstofdeeltjes gemeten in het milieu

Door de uitlaatgassen van dieselmotoren in het verkeer, komt elementair koolstof ook voor in het algemene milieu. In de lucht van Nederlandse steden variëren de concentraties elementaire koolstofdeeltjes tussen de 0,4 en 2 µg/m^3 – dus boven het streefrisiconiveau, en in sommige gevallen zelfs boven het verbodsrisiconiveau. Dat dieselmotoremissie niet alleen op werkplekken maar ook in het algemene milieu een gezondheidsrisico vormt voor mensen is niet nieuw, maar de afgeleide risicogetallen maken wel duidelijk dat werknemers niet hoger blootgesteld zouden mogen worden dan aan het achtergrondniveau.

Advies aan de minister

Voor de beroepsmatige blootstelling aan emissie van dieselmotoren in de werkomgeving, heeft de commissie risicogetallen afgeleid, die overeenkomen met een blootstellingniveau dat een extra kans geeft op overlijden aan longkanker van 4 op de 100.000 (streefrisiconiveau) en 4 op de 1.000 gevallen (verbodsrisiconiveau). De afgeleide risicogetallen zijn respectievelijk 0,011 µg inhaleerbare elementaire koolstofdeeltjes/m^3 en 1,03 µg inhaleerbare elementaire koolstofdeeltjes/m^3.

Omdat het blootstellingniveau dat overeenkomt met het verbodsrisiconiveau al wordt overschreden bij achtergrondniveaus in het algemene milieu adviseert de commissie dat blootstelling van werknemers niet hoger zou mogen zijn dan het achtergrondniveau.

Executive summary

At request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, derives so-called health-based calculated occupational cancer risk values (HBC-OCRVs) associated with excess cancer risk levels of 4 per 1,000 and 4 per 100,000 as a result of working life exposure to substances. It concerns substances which are classified by the Health Council or the European Union in category 1A or 1B, and which are considered stochastic genotoxic carcinogens. For the estimation, the Committee uses the *Guideline for calculating carcinogenic risks* of the Health Council.[1] In this report the Committee evaluates the possibility to establish such estimates for diesel engine exhaust. Diesel engine exhaust is a complex mixture of substances in gaseous and particulate phase, which is produced by the combustion of diesel fuels.

The Committee estimates that the concentration of elemental carbon (EC) from diesel engine exhaust in the air, which corresponds to an excess cancer risk level of

- 4 deaths per 1,000 (4×10^{-3}), for 40 years of occupational exposure, equals to 1.03 µg EC/m^3,
- And 4 deaths per 100,000 (4×10^{-5}), for 40 years of occupational exposure, equals to 0.011 µg EC/m^3.

Since the estimated HBC-OCRV of 1.03 µg EC/m^3 falls in the range of the ambient urban air levels in the Netherlands (0.4 – 2.0 µg EC/m^3), and the HBC-OCRV of 0.011 µg EC/m^3 is even far below these levels, the committee recommends that workers should not be exposed to diesel engine exhaust at levels higher than the background levels.

1 Scope

1.1 Background

At request of the minister of Social Affairs and Employment, the Dutch expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of chemical substances that are used in the workplace (Annex A). The purpose of these evaluations is to recommend health-based occupational exposure limits (HBROELs) or health-based calculated occupational cancer risk values (HBC-OCRVs) for the concentration of the substance in air, provided the database allows the derivation of such value. These recommendations serve as a basis in setting legally binding occupational exposure limit values by the minister.

In this advisory report, such a recommendation is made for diesel engine exhaust.

1.2 Committees and procedure

The current recommendation by the DECOS is based on an evaluation that was co-produced with the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The co-production is a result of an agreement between both groups to prepare jointly scientific criteria documents, which can be used by the national regulatory authorities in the Netherlands and the Scandinavian countries for establishing exposure limits. In 2016, the final evaluation was published by the Swedish National Institute of Occupational Health (in the Arbete och Hälsa series). It is available on the website of the Health Council.[2]

On the basis of the joint evaluation and additional evaluation of studies, the DECOS assessed whether for diesel engine exhaust an HBROEL or HBC-OCRVs could be recommended. The assessment and recommendation are described in the present advisory report.

The members of the DECOS are listed in Annex B.

In 2017, the president of the Health Council released a draft of this advisory report for public review. The individuals and organizations that commented on this draft are listed in Annex C. The committee has taken these comments into account in deciding on the final recommendation of the report. The received comments, and the replies by the Committee, are publicly available on the website of the Health Council.

1.3 Data

The committee´s recommendation is based on scientific data, which are publicly available, and which are presented and evaluated in the NEG-DECOS evaluation report. In addition, via PubMed additional data were retrieved up to September 2017.

2 Hazard assessment

2.1 Introduction

Diesel engine exhaust (DEE) is a complex mixture of substances in gaseous and particulate phase, which is produced during the combustion of diesel fuels. The main components of the gas phase of DEE are nitrogen, carbon dioxide (CO_2), oxygen, water vapor, nitrogen oxides (NO_x) and carbon monoxide (CO). Small amounts of sulphur dioxide (SO_2) and various organic compounds, such as low-molecular-weight carbonyls, may be emitted in the gas phase. DEE particulates contain elemental carbon (EC), organic compounds, sulphates, nitrates and metals and other elements.[2] The general population is exposed to DEE in ambient air due to road traffic. The working population may be additionally exposed to exhaust emitted by: on-road vehicles, off-road vehicles, sea-going and inland water vessels, locomotives, and stationary equipment (such as pumps and electricity generators).

In Europe, the past two decades increasingly stringent emission standards for diesel engines have been introduced for heavy- and light-duty engines, and non-road engines. For example, for heavy-duty diesel vehicle engines, emission of DEE particles was regulated from 0.36 g/kWh in 1992 to 0.01 g/kWh in 2013 (a 36-fold reduction over 20 years).[3] For non-road engines, that are most relevant for occupational exposures, the emission limits of diesel exhaust particles declined from 0.54-0.85 g/kWh in 1999 to 0.025 g/kWh in 2011-2014 for all engines with a power larger than 37 kW. For non-road engines with a power below 37 kW, a higher particle emission is allowed (0.6 g/kWh); for non-road engines smaller than 19 kW the emissions are not regulated. All standards apply only to new vehicles or engines. Consequently, exhaust composition of newer diesel engines with emission reduction systems differ from that of older diesel engines. The committee is of the opinion that it will take many years before the old diesel engines are replaced by newer ones, and therefore near future (occupational) exposure will still be related to traditional and transitional diesel engine technology.

2.2 Elemental carbon (EC) as exposure measure for DEE exposure

Because of the complex composition of DEE, varying indicators have been applied for the measurement of DEE exposure in workplaces. For the particulate phase of diesel exhaust, respirable particulate mass (PM_{10}, $PM_{2.5}$ and $PM_{1.0}$) and EC have been measured. For the gas phase of diesel exhaust, NO_x and CO are generally applied as exposure indicators.[2]

The committee prefers EC exposure because EC is considered to be a more specific and sensitive marker of DEE particles in the workplace than other substances. Especially in older diesel engines, EC forms a large part of the particulate mass. Furthermore, in most workplaces diesel engines are the only source of EC. The committee emphasizes that for new technology diesel engines (exhaust with significantly reduced particle mass and EC concentrations) EC may not be an equally useful marker.

2.3 Health-Based Calculated Occupational Cancer Risk Values

2.3.1 Critical effect

The adverse health effects caused by exposure to diesel engine exhaust was evaluated in the joint NEG-DECOS evaluation. Based on this evaluation, the committee considers cancer as the critical adverse health effect that should be prevented, because of the severity of the disease. Exposure to DEE in humans is associated with lung cancer and bladder cancer.

There is extensive epidemiological evidence for a causal association between occupational exposure to diesel exhaust and lung cancer. In 2012, the International Agency for Research on Cancer (IARC) classified diesel engine exhaust as carcinogenic to humans (Group 1: carcinogenic to humans).[4] IARC concluded that diesel engine exhaust is a cause of lung cancer based on human, animal and experimental evidence. Also in the Netherlands, DEE is listed as a carcinogen.[5] In the joint evaluation all identified cohort and case-control studies related to lung cancer were summarized (see table 19 and 20 in the NEG-DECOS evaluation).[2] Most studies focused on lung cancer in combination with job title or years of work. The majority of these studies found significantly positively associations with risk ratio's generally between 1.3 and 1.6. But higher risks have been found in some studies among the highest exposure groups.
For bladder cancer, there is some evidence for an association with DEE exposure. Increased risk for bladder cancer was noted in some case-control studies, but not in cohort studies. Furthermore, part of the studies had methodological shortcomings in that for instance no adjustments were made for smoking.

There is strong mechanistic evidence that diesel engine exhaust, as well as many of its components, can induce lung cancer in humans through stochastic genotoxic mechanisms, including: DNA damage, gene and chromosomal mutations, changes in relevant gene expression, the production of reactive oxygen species and inflammatory responses[4]. In addition, the co-carcinogenic, cell-proliferative and/or tumor-promoting mechanism probably contributes to its carcinogenicity in the human lung. Based on

these data, the committee is of the opinion that DEE is a genotoxic carcinogen with a stochastic mechanism of action. For stochastic genotoxic compounds the quantitative risk assessment involves deriving a Health-Based Calculated Occupational Cancer Risk Value (HBC-OCRV).

Such an HBC-OCRV should prevent or limit any kind of other adverse health effects. In addition to lung and bladder cancer, exposure to diesel exhaust is amongst others also associated with inflammatory lung effects. In inhalation studies among human healthy volunteers, pulmonary inflammatory effects occurred at the lowest tested concentration of 100 µg diesel exhaust particles/m^3 for 1 to 2 hours (see studies summarised in table 21 in the NEG-DECOS evaluation).[2] The committee is of the opinion that these studies are not useful for quantitative risk assessment as the inhalation studies in human volunteers were designed to study the nature of the inflammatory response after a short-term single exposure event, and not to assess the shape of the exposure response curve. Therefore relatively high EC levels were chosen. As a result, one cannot conclude that there is no inflammation at levels below 100 µg diesel exhaust particles/m^3, since there is a lack evidence in that range for longer periods of exposure. A No Observed Adverse Effect Concentration for respiratory effects was therefore not derived.

In addition to the adverse health effects in the lungs, exposure to DEE in humans is associated with respiratory inflammation and adverse cardiovascular effects. Furthermore, it is suggested that exposure may exacerbate respiratory disorders, such as asthma, and allergic diseases. Although the available data is limited and mainly based on animal experiments or studies in the general population, some evidence for adverse neurophysiological symptoms, immunologic effects, and reproductive and developmental effects have been described. A detailed evaluation of these types of effects was given in the joint evaluation.[2]

2.3.2 Selection of studies suitable for risk estimation in the workplace

The committee prefers the use of epidemiological data for the calculation of cancer risk values, because epidemiological data do not involve the uncertainties associated with biological differences between animals and humans, and the exposure conditions in epidemiological studies are generally representative for the exposure in the occupational setting.

In calculating occupational cancer risk values, quantitative exposure-response relationships are needed. For lung cancer, these are available. In total four epidemiological studies describe the exposure-response relationship between lung cancer mortality and (retrospective) quantitative estimates of diesel exposure

measured by EC as exposure indicator.[6-9] One of these studies, conducted by Möhner et al., is hampered by the high exposure levels of the reference group.[7] Therefore the committee decided that this study was not suitable for quantitative risk assessment. The quality of the remaining three studies was sufficient and useful for quantitative risk assessment.[6,8,9] All three studies showed positive associations and trends between cumulative EC exposure and lung cancer mortality. Detailed information of the three studies is summarized in Annex D. The committee evaluated the three studies on quality and usefulness for quantitative risk assessment, which is described in the following paragraphs.

The oldest study is a nested case-control study performed by Steenland et al. among workers in the US trucking industry (994 lung cancer deaths (based on death certificates), and 1,085 controls).[6] Cases and controls were divided by job-categories. In 1988 and 1989 sub-micrometer EC was measured in 242 samples covering the major job categories. To estimate past exposure, the assumption was made that extrapolation over time is proportional to the number of trucks on the road, the particulate emission of diesel engines over time, and leaks from trucks exhaust systems for long-haul drivers. Historical levels of exposure were linked to known work history. Due to a lack of data, it was not possible to evaluate the assumptions that were made to estimate past exposure, however, the committee considers the assumptions reasonable. Three different exposure scenario 's (most plausible, low and highest estimate of exposure) were considered, and resulted in exposure coefficients that remained in a relatively narrow range (from 0.0002 to 0.0008). The authors used logistic regression analysis to assess the association between EC exposure and lung cancer mortality. The analyses were adjusted for age, race, smoking, diet and self-reported asbestos exposure.

Another study among US trucking industry workers was a retrospective cohort study performed by Garshick et al.[9] In total 31,135 work records were available of male workers employed in the US trucking industry in 1985. Lung cancer mortality was ascertained through the year 2000 (779 lung cancer deaths). From 2001 to 2006 a detailed exposure assessment to submicron EC was conducted (> 4,000 measurements, stationary samples, personal samples and background samples). Exposure models were developed to estimate exposure nationally and historically.[10] The historical exposure estimates included changes in job-related exposure over time, and historical changes in background air pollution (represented by the coefficient of haze, which is predictive of ambient EC) and fuel use. Analyses were conducted via proportional hazard regression analysis. Multiple exposure metrics were evaluated namely: time-dependent cumulative exposure modeled in lags of 0, 5 and 10 years, and time-dependent average exposure modeled in lags of 0 and 5 years. The full cohort was analysed, and a cohort excluding the mechanics. For mechanics, validity of

extrapolation of current exposure to historical estimates was indicated not to be valid due to changing job duties. Garshick et al. used an adjustment method for healthy worker survivor bias by using duration of employment. Without this adjustment, strong evidence of a trend in the exposure-response was lacking. Cumulative exposure contains already a measure of duration, which can lead to over-adjustment. The committee is of the opinion that this adjustment makes comparison with other studies difficult. However, it is not a reason to exclude the study for quantitative risk assessment. The results of Garshick et al. were not adjusted for smoking due to a lack of data. In a previous study, the authors estimated the potential impact of smoking by job group, which indicated that smoking is not a major explanation for the associations between EC exposure and lung cancer in this cohort.[11]

The National Institute for Occupational Safety and Health (NIOSH) and National Cancer Institute (NCI) conducted a study among mine workers.[12] In this study population, Silverman et al. studied quantitative exposure to EC and lung cancer mortality.[8] The study consisted of a cohort mortality study, and a nested case-control study of lung cancer mortality. Results of the cohort and nested case-control study were consistent, both showing an exposure-response association. As the nested case-control study had adjusted for smoking habits, the committee used results from this study for quantitative risk assessment. This study was nested within a cohort of 12,315 workers in non-metal mining facilities. In total, 198 lung cancer deaths and 562 incidence density-sampled control subjects were included. Between 1998 and 2001, a detailed exposure assessment to respirable EC was conducted. Based on these measurements, location- and job title-specific estimates were developed. Modeled historical trends in carbon monoxide levels, which were based on horsepower use and ventilation, were used for back extrapolation of respirable EC measurements from 1998-2001 to estimate historical annual average daily respirable EC levels.[13] Logistic regression was used to assess the association between respirable EC exposure and lung cancer mortality. Crump et al.[14] extended the analyses of the study by Silverman et al. by developing six alternative models for estimating historical measures of respirable EC exposure.[8] These additional sensitivity analyses demonstrated robustness in the association of lung cancer mortality and alternative estimates of respirable EC. The only exception was that a sensitivity analyses with additional adjustment for radon (a well-known human carcinogen) resulted in a much weaker effect of respirable EC on lung cancer mortality. In an extensive evaluation, the HEI discussed the validity of the possibility that radon may have contributed to at least a portion of the lung cancer burden among underground miners.[15] The HEI concluded that “radon exposure was not critically important and could itself lead to unintended bias”. This conclusion was based on the fact that the radon levels in the underground mines were well below the current standards as set by the American National Institute for Occupational Safety and Health (Recommended Exposure Limit), the Mine Safety

and Health Administration standard, and the Occupational Safety and Health Association (Permissible Exposure Limit). Furthermore, the concentration of radon is expressed as the level of radon plus the duration of employment. Since the levels of airborne radon in underground mines are relatively constant, this indicates a strong correlation between cumulative concentration of radon and duration of exposure. The correlation between the concentration of EC and duration is less strong, because the levels of EC are more variable and cumulative exposure of EC is therefore less dependent on the duration. It is almost impossible to disentangle the cumulative exposure to EC and radon in a sensitivity analyses; instead it weakens the validity of it. The committee agrees with the findings of the HEI. Based on these arguments, the committee is of the opinion that adjustment for radon implicates an over-correction and thus is not necessary.

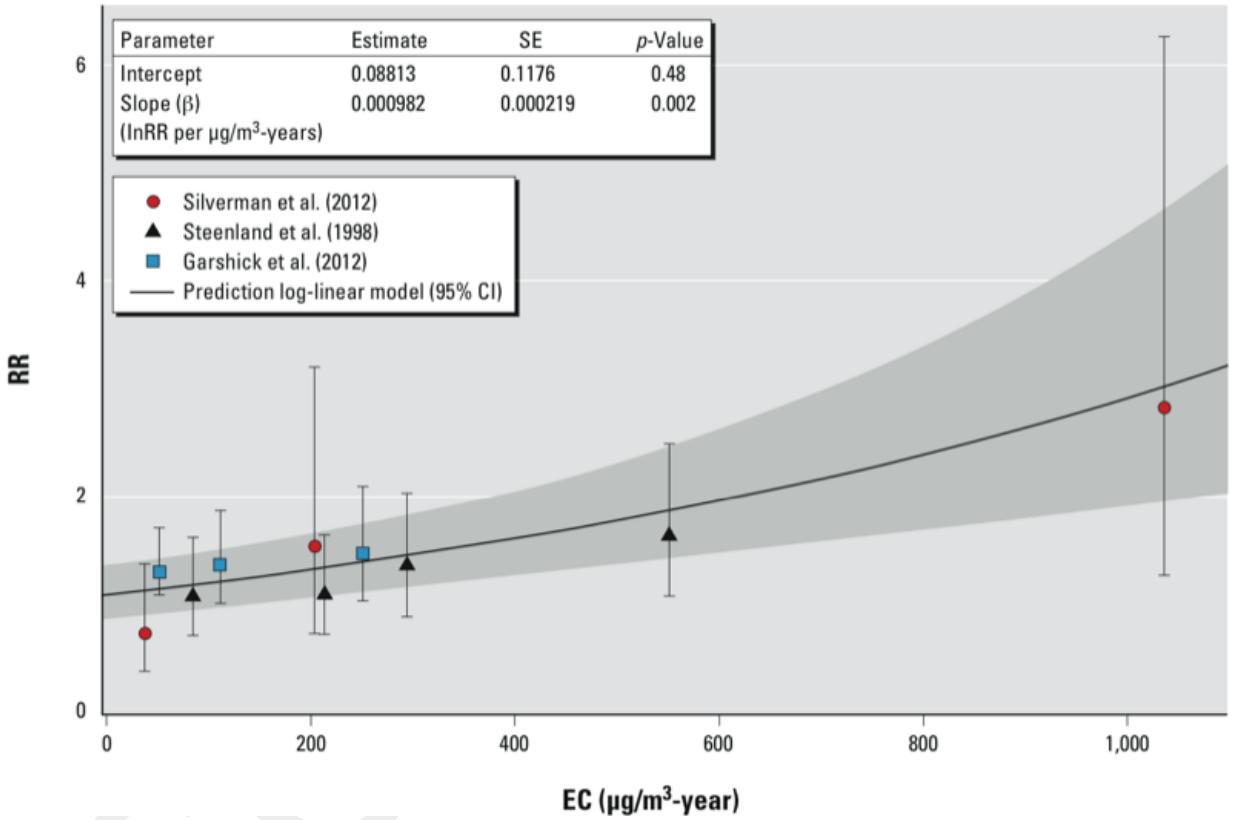
The three studies with quantitative exposure estimates have been discussed extensively in the literature.[14-17] The comments deal with a) general issues in the data analysis (adjustment for the healthy worker effect by duration of tenure), b) adjustment for confounders (smoking, radon), c) measurement of exposure, and d) exposure reconstruction and estimation. Recognizing the above mentioned limitations and uncertainties of the three studies, the committee is of the opinion that data of all three studies provide a useful basis for quantitative risk assessment of exposure to diesel engine exhaust. In addition, the Health Effect Institute (HEI) reviewed two of these studies (Garshick et al. and Silverman et al.), and assessed the utility of both studies for quantitative characterization of the exposure-response relationship between DEE and lung cancer.[8,9,15] HEI concluded that both studies were well-designed and well-conducted, and could provide a good starting point for a quantitative risk assessment. The committee emphasizes that the human epidemiological studies reviewed were conducted before the introduction of modern diesel engine technology, therefore risk assessment results relate to older diesel engines.

2.3.3 Meta-regression analyses

A meta-analysis integrates findings from different individual studies to obtain a more powerful and reliable exposure-response relationship. One meta-regression study has been performed by Vermeulen et al. (2014).[18] This analysis was included the three before mentioned epidemiological studies on the association between DEE exposure, expressed as cumulative exposure to EC in µg/m^3-years, and lung cancer mortality.[6,8,9] In the meta-analysis a common exposure-response curve for diesel engine exhaust was predicted. Vermeulen et al. (2014) extracted in total 10 study-specific categorical relative risk estimates for lung cancer mortality in association with DEE exposure relative to the lowest exposure category.[18] The midpoint of each exposure category was used as a specific estimate of cumulative exposure for each relative risk. The

midpoint of the highest exposure category was estimated as 5/3 times the lower bound of the category. The combined slope estimate, i.e. the natural logarithm of the relative risk (lnRR) estimated for a 1 µg/m^3- year increase in cumulative EC, was 0.000982 (95% confidence interval: 0.00055 – 0.00141) for lung cancer mortality, and was based on a log-linear meta-regression model. Figure 1 shows the predicted exposure-

Figure 1. Predicted exposure –response curve of cumulative elemental carbon (EC) and lung cancer risks (mortality) based on a log linear model using relative risk (RR) estimates from three cohort studies[6,8,9]



derived by Vermeulen et al.(2014).[18] SE, standard error; 95% CI, 95% confidence interval.

response curve using relative risk (RR) estimates from the three epidemiological studies. The dark grey shaded area presents the 95% confidence interval estimates. Slope estimates of the three studies included in the meta-analysis were within a factor two, and confidence intervals were overlapping. Sensitivity analyses were conducted by using alternative risk estimates of one of the three studies, while keeping information of the other two studies unchanged. Also two sensitivity analyses were included with estimates from the study of Möhner et al., which was not included in the original analyses due to methodological short comings.[7] Combined slope estimates based on the sensitivity analyses were generally consistent.

The three epidemiological studies with quantitative exposure estimates were conducted in populations of the United States (US). Epidemiological studies on lung cancer and job title/years worked (see table 19 and 20 NEG-DECOS evaluation)[2] conducted in the European population show comparable effects as studies in the US population. Therefore, the committee considers the results of the meta-regression generalizable for the European population.

The meta-regression of Vermeulen et al. has been discussed in the literature.[16,17] The comments generally pertain to: 1) quality of the input data for primary analysis (adjustment for duration, adjustment for radon, re-categorizing data);[7-9] 2) heterogeneity between used studies for input data; 3) general issues in the data analyses (meta-regression used mixed data from exposure lagged 5 years and 15 years); and 4) analytical methods applied (fixed and random effects regression analyses). Despite these critical comments, the committee is of the opinion that the meta-regression of Vermeulen et al. is the best starting point in estimating an HBC-OCRV in humans who are occupationally exposed to diesel engine exhaust. One reason is the completeness of the meta-analyses with its subanalyses. Furthermore, the meta-analysis is performed according to the current standards. Also the committee considers the exposure-response data from the three individual cohort studies on which the meta-analysis is based, of sufficient quality to be used in quantitative risk analysis.

The committee prefers to use incidence statistics over mortality statistics for two reasons: 1) working conditions policy is primarily focused on protecting employees from the occurrence of disease, regardless of mortality, and 2) registration of morbidity is generally more reliable than registration of mortality data. The three epidemiological studies used by Vermeulen et al. were all based on mortality statistics.[6,8,9,18] However, since life expectancy after lung cancer diagnosis is low, use of mortality instead of incidence data will have minor effect on cancer risk values calculation. Therefore, the committee considers these data suitable in assessing an HBC-OCRV.

2.3.4 Calculation of the HBC-OCRV

Based on the exposure-response relationship calculated in the meta-analysis by Vermeulen et al. (2014; see figure 1), an HBC-OCRV can be estimated. A cancer risk value is an exposure level (a concentration in the air) corresponding with a (by the government) predefined extra risk of developing cancer. In the Netherlands, the predefined extra risks on which the HBC-OCRVs should be based are 4 extra cases of lung cancer death due to 40 years of occupational exposure per 1,000 (4×10^{-3}) and 100,000 (4×10^{-5}) cases of death (all causes) in the general population. For example, in the Dutch general population, in 2015 about 73 per 100,000 men died of lung cancer

(source Statistics Netherlands). Theoretically, an HBC-OCRV corresponding to 4 extra cases of lung cancer death per 100,000 cases of death in the general male population, should than be based on a relative risk of 1.055 ((73 + 4)/73; excess risk 0.055).

Alternatively, in assessing relative risks, the committee prefers using life-table analyses. By using life tables, death due to other causes can be accounted for. Furthermore, life-table analysis makes it possible to account for time and age-dependent factors in the development of cancer, such as latency. In the Guideline for the calculation of occupational cancer risk values, the committee gives detailed information on the use of this type of analysis.[1] In short, the concept of life-table analyses is to compare lung cancer mortality in two hypothetical birth cohorts of equal size. The first cohort is only exposed to background exposure, and the second to occupational DEE exposure resulting in elevated lung cancer mortality from DEE. Occupational exposure starts at the age of 20 and gradually builds up till the age of 60. The cohorts gradually reduce in size because of lung cancer mortality and mortality due to other causes of death. Excess risk calculations were truncated at the age of 100, assuming that deaths occurring beyond this age are unlikely to be related to occupational DEE exposure. Information on the average population size and number of deaths from all causes and from lung cancer in 5-year age categories for the Dutch population during 2000-2014 was obtained from Statistics Netherlands (available online: www.cbs.nl). Using the life-table analysis with data from the Dutch population, Vermeulen et al. (2016) estimated relative risks of 1.041 and 1.0004 (rounded off) per 1,000 and per 100,000 cases, respectively.

The concentrations of EC, which corresponds to these relative risks, can be calculated using the log-linear model equation that describes the exposure-response relationship (adopted from figure 1):

lnRR = intercept + slope (β) x exposure

in which: lnRR is the natural logarithm (ln) of the relative risk (RR); the intercept is set at zero; the slope (β) is 0,000982, and the exposure is expressed as cumulative exposure concentration (µg/m^3-years) after 40 years of occupational exposure. An HBC-OCRV (expressed as average concentration) is obtained by dividing the cumulative exposure concentration by 40 (years).

Applying the estimated relative risks in this equation, the committee estimated that the concentration of EC in diesel engine exhaust, which corresponds to an excess cancer risk of

- 4 deaths per 1,000 (4×10^{-3}), for 40 years of occupational exposure, equals to 1.03 µg EC/m^3,

- and 4 deaths per 100,000 (4×10^{-5}), for 40 years of occupational exposure, equals to 0.011 µg EC/m^3.

Additional sensitivity analyses

Vermeulen et al.[19] conducted additional sensitivity analyses which were proposed by themselves and others[17]. Sensitivity analyses were conducted by using alternative risk estimates of one of the three studies, while keeping information of the other two studies unchanged. For example, from the study by Garshick et al.[9] hazard ratio's were used from unlagged and 10 years lagged analyses (versus 5 years lagged data from main analyses), and hazard ratio's based on analyses that included mechanics. From the study by Silverman et al.[8], odds ratio's were used based on unlagged data (versus 15 years lagged data), and a sensitivity analyses was performed with odds ratios excluding the highest quartile of exposure. From the study by Steenland et al.[6] odds ratios for unlagged exposure (versus 5-year lagged data) were used for sensitivity analyses. In addition, sensitivity analyses were also conducted excluding the study of Garshick, and only including one of the three studies separately. These different analyses resulted in alternative slope factors which varied between 0.0006 and 0.0012. Exposure limits based on these slopes ranging between 0.009-0.017 and 0.85-1.67 µg/m^3 for the acceptable risk and maximum tolerable risk, respectively. Results of the sensitivity analyses indicates that exposure limits were generally consistent.

2.3.5 Occupational and ambient air levels of elemental carbon

Occupational exposure levels to diesel engine exhaust vary between jobs (studies on occupational exposures are summarized in tables 2 to 5 in the joint NEG-DECOS evaluation)[2]. In the Netherlands, the highest occupational exposure levels (average 20 – 50 µg EC/m^3) were reported for employees on ferries, mechanics (working out- and inside), employees in container ports, trans-shipment, distribution and auctions, and workers in garages. Garbage men, road workers, ground personell in airports and workers in bus depots are on average exposed to 10 – 20 µg EC/m^3. Lower exposure levels have been measured in the agricultural and construction industry, and for professional drivers (5 – 10 µg EC/m^3).[20] Ambient air levels of EC in urban areas in the Netherlands were between 0.4 and 2 µg EC/m.[213 22-25]. This means that the estimated HBC-OCRV of 1.03 µg/m^3 falls in the range of ambient urban air levels, and the estimated HBC-OCRV of 0.011 µg/m^3 falls far below these levels. The finding is not unexpected since data on traffic-related air pollution and adverse health effects in the general population show that at these background levels increased risks exist for respiratory and cardiovascular mortality.[26-29] The foregoing implies that workers should not be exposed to diesel engine exhaust at levels higher than the background levels

2.4 Conclusion and recommendation

The Committee estimates that the concentration of elemental carbon (EC) from diesel engine exhaust in the air, which corresponds to an excess cancer risk of

- 4 deaths per 1000 (4×10^{-3}), for 40 years of occupational exposure, equals to 1.03 µg EC/m^3,
- And 4 deaths per 100,000 (4×10^{-5}), for 40 years of occupational exposure, equals to 0.011 µg EC/m^3.

Since the estimated HBC-OCRV of 1.03 µg EC/m^3 falls in the range of ambient urban air levels in the Netherlands (0.4 – 2.0 µg EC/m^3), and the HBC-OCRV of 0.011 µg EC/m^3 far below these levels, the committee recommends that workers should not be exposed to diesel engine exhaust at levels higher than these background levels.

2.5 Groups at risk

Subjects with chronic respiratory or cardiovascular diseases are likely to be more sensitive to the health impacts of DEE. Exposure to DEE may exacerbate pre-existing cardiovascular diseases and respiratory disorders including asthma.

2.6 Research needs

Numerous studies have been published on the adverse health effect of diesel exhaust. However limited data are available on quantitative exposure-response relationships. The meta-regression analysis, which was used in estimating an HBC-OCRV, was based on observational studies conducted before the introduction of modern diesel engine technology. Therefore, results relate to older diesel engines. In addition, emission regulations have caused a change in composition of diesel exhaust. For example, the proportion NO_2 and NO differs in the exhaust of new technology diesel engines, in that NO_2 may account for up to 50% of NOx. Also it is unknown what kind of adverse health effects the emission by these new engines may cause, which requires more short- and long-term studies. Furthermore, technology trends are converging to electric engine development, especially in automobile transportation. Despite this trend, the committee expects that it will take many years before electric engines replace all diesel engines, especially for heavy-duty use. Therefore, studies on adverse health effects of the exhaust from new technology diesel engines will stay relevant.

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Annexes

A Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:
The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice.
- If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.
- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B

B The committee

- F.G.M. Russel, *chairman*
  Professor of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen
- D.J.J. Heederik
  Professor of Risk Assessment in Occupational Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R. Houba
  Occupational Hygienist, Netherlands Expertise Centre for Occupational Respiratory Disorders, Utrecht
- H. van Loveren
  Professor of Immunotoxicology, Maastricht University, Maastricht
- I.M.C.M. Rietjens
  Professor of Toxicology, Wageningen University and Research Centre, Wageningen
- G.B.G.J. van Rooy
  Occupational Physician/toxicologist, Arbo Unie Expert Centre for Chemical Risk Management, and Radboud UMC Outpatient Clinic for Occupational Clinical Toxicology, Nijmegen
- RA Woutersen,
  Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- P.J. Boogaard, *consulted expert*
  Professor in of Environmental Health and Human Biomonitoring, Wageningen University and Research Centre; and toxicologist, Shell International BV, The Hague
- R.C.H. Vermeulen, *consulted expert*
  Epidemiologist, Institute for Risk Assessment Sciences, University Utrecht, Utrecht
- A.H. Piersma, *structurally consulted expert*
  Professor of Reproductive and Developmental Toxicology, Utrecht University, and National Institute for Public Health and the Environment, Bilthoven
- H. Stigter, *observer*
  Occupational Physician, Inspectorate SZW, Ministry of Social Affairs and Employment, The Hague
- G. Van Essen, *observer*
  Social and Economic Council, The Hague
- J.M. Rijnkels, *scientific secretary*
  Scientific secretary, Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. For each substance to be evaluated, the members are asked about their potential conflicts of interest. An expert with a personal financial interest cannot be a member of the Committee. In case of other, less clearly marked interests, experts can be consulted as non-members when their expertise is considered essential for the advisory report. By law, an expert working at an organization that is part of a Ministry cannot be a member of a Health Council Committee. Such an expert can be consulted as a non-member when there are no conflicting interests involved. It is the responsibility of the President of the Health Council, after consulting the chairman of the Committee, to assess the interests indicated and decides on the consequences for a possible membership.

C Comments on the public review draft

A draft of the present advisory report was released in October 2017 for public review. The following organizations and persons have commented on the draft:

- …

D Critical observational studies

	Steenland et al. 1998	Garshick et al. 2012	Silverman et al. 2012
Study design and population			
Design	Nested case-control	Retrospective cohort (Trucking Industry Particle Study or the Truckers study)	Nested case-control (DEMS-study)
Country	USA	USA	USA
Study period/period of data collection	1949 (year that diesel fuel began te be used in appreciable quantities) – 1990; exposure analyses based on data of 1983	1985 - 2006	1947 (introduction diesel equipment) - 1997
Type of industry	Trucking industry	Trucking industry	Mining industry (non-metal)
Job categories	Long-haul drivers (N=1,237) Short-haul drivers (N=297) Dockworkers (N=164) Mechanics (N=88) Those outside trucking industry (N=120 + N=30 added because of retirement in trucking industry before 1949)	*Drivers*: long-haul, pick-up & delivery dockworkers *Hostler, non-drivers*: dockworkers, mechanics, clerks, other	Workers in limestone, potash, salt or trona mines; both underground and surface mining
Source study population	Members of Central States Teamsters Union (N=10,699)	Members of Teamsters Union in four companies (N=58,326)	8 mining facilities with at least 50 employees (N=12,315) These mines were chosen because of known low exposure to other potential lung cancer substances than DEE (including radon, silica, asbestos and PAHs)
Selection population	*Cases* (N=994): all lung cancer deaths in 1982-1983 *Controls* (N=1,085): every sixth death from files of Central States Teamsters Union; excluding lung cancer deaths, bladder cancer, and deaths due to accidents *Reference* (N=150): those outside the trucking (not exposed)	31,135 workers 29,324 without mechanics	*Cases* (N=189): all lung cancer deaths *Controls* (N=562): matched on mining facility, sex, race/ethnicity, birth year
Inclusion criteria	Worked any time in job category after 1959	Employed in 1985 Member of Union Employed for at least 1 yr Males Age ≥ 40 yrs in 1985	Low levels of radon, silica and asbestos exposure Employed for at least 1 yr after introduction of diesel equipment (1947-1967)

Average age at start of study/data collection	n/a	1985: 49.1 ± 6.0 yrs	n/a
Work history	Average years in jobs (cases and controls): approximately 23-24 years Source: Teamster Union Work History	Years of work: < 10 yrs: 2,950 10 to <20 yrs: 10,443 20 to <30 yrs: 12,202 ≥ 30 yrs: 5,540 Mean yrs of work: 21.6	
Original study	Case-control study (Steenland et al. 1990)	Retrospective cohort study (Laden et al. 2007)	Cohort (Coble et al. 2010; Stewart et al. 2010, 2012; Vermeulen et al. 2010a, 2010b)
Exposure assessment			
Marker diesel engine exhaust exposure	Sub-micrometer elemental carbon (EC_{sub}), cumulative	Elemental carbon (EC), cumulative and average	Respirable elemental carbon (REC), cumulative and average
Exposure assessment	Historical levels of exposure linked to known work history	Historical exposure linked to work records to estimate personal exposure	No data
Historical exposure assessment	Data on changes in diesel engine over time, period 1949 – 1990 EC_{sub} measured in 242 samples covering major job categories, ambient roadway and non-roadway levels Assumption (1): Ambient exposure increased in proportion to the use of diesel engines Assumption (2): use of heavy duty trucks is a good marker of diesel engine use (expressed in vehicle miles travelled)	Based on the national assessment for EC exposure; data on historical trends ambient terminal EC available from period 1971 -2000; approach validated with data from 1988-1989; model accounted for changes in job-related exposures (1988-1989 compared to 2001-2006)	Estimates based on measurements from 1998 – 2001 DEMS industrial hygiene surveys, past Mine Safety and Health Administration enforcement surveys, other measurement data, company records, interviews with long-term workers
Current exposure assessment	n/a	Period: 2001 – 2006; stationary samples at different locations, personal samples, and ambient background samples; separate exposure models used for drivers and terminal workers	n/a
Personal exposure estimation	Assumption (1): average 1990 levels for job category could be assigned to all subjects in that category Assumption (2): levels prior to 1990 were proportional to vehicle moles travelled by heavy duty trucks and the estimated emission levels	From date of hire – end of 2000; time-dependent cumulative exposure modelled in lags of 0, 5 and 10 years; time-dependent average exposure modelled in lags of 0 and 5 years	Time-dependent exposure modelled in lags of 0, 3, ..., 25 years with 2-year intervals. Optimal lag-interval of 13-17 years for average exposure Optimal lag-interval of 15 years for cumulative exposure Final analyses: unlagged and

	Assumption (3): long-haul drivers received some exposure from their own truck Time-dependent cumulative exposure modelled in lags of 0 and 5 years		15-year lag
Other issues	Assumption (1): background exposure in ambient air was 1 µg/m^3 per year. This was added to everyone's cumulative exposure	Office workers: background exposure Sub-analysis performed excluding mechanics (N = 1,811)	Also risk analyses performed on exposure to radon, asbestos, silica, PAH (non-diesel sources) and respirable dust. Analyses revealed no excess lung cancer risk for any of these substances
Cumulative exposure	Median (all job categories) 372,9 (range 0.45 – 2,439.9) µg/m^3-years Median (all job categories) 442.1 (range 57.4 – 2,497.9) µg/m^3-years (including background levels)	With / without mechanics *Minimum (µg/m^3-months)*: No lag : 10 / 10 5-yr lag : 0 / 0 10-yr lag: 0 / 0 *Maximum (µg/m^3-months)*: No lag : 24,130 / 15,242 5-yr lag : 24,130 / 15,074 10-yr lag: 23,106 / 10.341	No data
Health effect assessment			
Data source mortality	Death certificates	National Death Index 1985 - 2000	National Death index Plus linked with Social Security Administration mortality files 1947 - 1997
Cancer type	Lung cancer (ICD code 162 or ICD code 163)	Primary lung cancer (ICD-9, code 162; ICD-10, codes C33-C34)	Lung cancer (ICD-O, code 162); part of the cases (70/170) based on pathology reports; interviews with next of kin (213/217)
Effect endpoint	Lung cancer death	Lung cancer death: 779 cases (734 underlying cause) Total number of deaths: 4,306	Lung cancer death
Exposure-response relationship			
Method	Logistic regression	Proportional hazard regression	Conditional logistic regression
Adjustments	Smoking habits, age, potential asbestos exposure	Age, lung cancer secular trends, race, census region of residence	Smoking habits, history of employment in high-risk occupations for lung cancer, history of respiratory diseases)
Sensitivity analysis	Total duration of employment	Total duration of employment	No data
Association with average exposure	No data	HR, hazard ratio $^{U/A}$ unadjusted/adjusted for duration of work	OR, Odds ratio CI, 95% confidence interval N = cases/controls

		CI, 95% confidence interval N = number of cases **5-year lag, all workers** *< 3.6 µg/m³ (*N=146): HR^{U} = 1.00 (reference) HR^{A} = 1.00 (reference) *3.6 - 5.4 µg/m³ (N=211):* HR^{U} = 1.15 (CI 0.93 – 1.43) HR^{A} = 1.15 (CI 0.93 – 1.43) *5.4 - 7.9 µg/m³ (N=221):* HR^{U} = 1.11 (CI 0.89-1.39) HR^{A} = 1.12 (CI 0.90 – 1.40) *≥ 7.9 µg/m³ (N=201):* HR^{U} = 1.06 (CI 0.84 – 1.34) HR^{A} = 1.08 (CI 0.85 – 1.36) *p* for trend^{U} = 0.97 *p* for trend^{A} = 0.88 **5-year lag, without mechanics** *< 3.6 µg/m³ (*N=146): HR^{U} = 1.00 (reference) HR^{A} = 1.00 (reference) *3.6 - 5.4 µg/m³ (N=211):* HR^{U} = 1.15 (CI 0.93 – 1.43) HR^{A} = 1.15 (CI 0.93 – 1.43) *5.4 - 7.9 µg/m³ (N=221):* HR^{U} = 1.11 (CI 0.89 – 1.39) HR^{A} = 1.12 (CI 0.89 – 1.40) *≥ 7.9 µg/m³ (N=163):* HR^{U} = 1.11 (CI 0.87 – 1.43) HR^{A} = 1.13 (CI 0.88 – 1.44) *p* for trend^{U} = 0.61 *p* for trend^{A} = 0.53	**No lag, all workers** *0 – 1 µg/m³ (N=49/166)*: OR = 1.00 (reference) *1 – 32 µg/m³ (N=50/207)*: OR = 1.03 (CI 0.50 – 2.09) *32 – 98 µg/m³ (N=50/207)*: OR = 1.88 (CI 0.76 – 4.66) *≥ 98 µg/m³ (N=50/207)*: OR = 2.40 (CI 0.89 – 6.47) *p* for trend = 0.025 **No lag, underground workers** *0 – 39 µg/m³ (N=29/89)*: OR = 1.00 (reference) *39 – 71 µg/m³ (N=29/57)*: OR = 1.91 (CI 0.91 – 4.01) *71 – 147 µg/m³ (N=29/66)*: OR = 2.38 (CI 1.04 – 5.44) *≥ 147 µg/m³ (N=29/52)*: OR = 3.69 (CI 1.40 – 9.70) *p* for trend = 0.010 **15-year lag, all workers** *0 – 1 µg/m³ (N=47/190)*: OR = 1.00 (reference) *1 – 32 µg/m³ (N=52/187)*: OR = 1.11 (CI 0.59 – 2.07) *32 – 98 µg/m³ (N=49/141)*: OR = 1.90 (CI 0.90 – 3.99) ≥ 98 µg/m^3 (N=50/148): OR = 2.28 (CI 1.07 – 4.87) *p* for trend = 0.062 **15-year lag, underground workers** *0 – 8 µg/m³ (N=29/81)*: OR = 1.00 (reference) *8 – 49 µg/m³ (N=29/73)*: OR = 1.04 (CI 0.45 – 2.43) *49 – 104 µg/m³ (N=29/58)*: OR = 2.19 (CI 0.87 – 5.53) ≥ 104 µg/m^3 (N=29/52): OR = 5.43 (CI 1.92 – 15.31) *p* for trend = 0.001
Association with cumulative exposure	OR, odds ratio CI, 95% confidence interval	HR, hazard ratio $^{U/A}$ unadjusted/adjusted for	OR, Odds ratio CI, 95% confidence interval

	No lag 0 -174 µg/m^3-years: OR = 1.20 (CI 0.79 – 1.81) 174 – 268 µg/m^3-years: OR = 1.16 (CI 0.77 – 1.75) 268 – 360 µg/m^3-years: OR = 1.39 (CI 0.91 – 2.11) > 360 µg/m^3-years: OR = 1.72 (CI 1.11 – 2.64) *p* for trend = 0.048 **5-year lag** 0 -169 µg/m^3-years: OR = 1.08 (CI 0.72 – 1.63) 169 – 257 µg/m^3-years: OR = 1.10 (CI 0.74 – 1.65) 257 – 331 µg/m^3-years: OR = 1.36 (CI 0.90 – 2.04) > 331 µg/m^3-years: OR = 1.64 (CI 1.09 – 2.49) *p* for trend = 0.032	duration of work CI, 95% confidence interval N = number of cases **No lag, all workers** < *530 µg/m^3-m (*N=153): HR^U = 1.00 (reference) HR^A = 1.00 (reference) *530 - 1,061 µg/m^3-m (N=194):* HR^U = 1.13 (CI 0.90 – 1.42) HR^A = 1.24 (CI 0.98 – 1.57) *1,061 - 2,076 µg/m^3-m (N=209):* HR^U = 1.14 (CI 0.89 – 1.47) HR^A = 1.30 (CI 0.99 – 1.70) *≥ 2,076 µg/m^3-m (N=223):* HR^U = 0.98 (CI 0.74 – 1.29) HR^A = 1.16 (CI 0.86 – 1.57) *p* for trend^U = 0.37 *p* for trend^A = 0.92 **No lag, without mechanics** < *530 µg/m^3-m (*N=153): HR^U = 1.00 (reference) HR^A = 1.00 (reference) *530 - 1,061 µg/m^3-m (N=193):* HR^U = 1.13 (CI 0.90 – 1.42) HR^A = 1.25 (CI 0.99 – 1.60) *1,061- 2,076 µg/m^3-m (N=202):* HR^U = 1.13 (CI 0.87 – 1.46) HR^A = 1.30 (CI 0.99 – 1.72) *≥ 2,076 µg/m^3-m (N=193):* HR^U = 1.02 (CI 0.76 – 1.36) HR^A = 1.24 (CI 0.89 0 1,71) *p* for trend^U = 0.63 *p* for trend^A = 0.71 **5-year lag, all workers** < *371 µg/m^3-m (*N=122): HR^U = 1.00 (reference) HR^A = 1.00 (reference) *371 - 860 µg/m^3-m (N=193):* HR^U = 1.18 (CI 0.92 – 1.51) HR^A = 1.30 (CI 1.01 – 1.68) *860 - 1,803 µg/m^3-m (N=208):* HR^U = 1.16 (CI 0.88 – 1.53) HR^A = 1.35 (CI 1.01 – 1.81)	**No lag, all workers** *0 – 19 µg/m^3-y (N=49/151)*: OR = 1.00 (reference) *19 – 246 µg/m^3-y (N=50/214)*: OR = 0.87 (CI 0.48 – 1.59) *246 – 964 µg/m^3-y (N=49/147)*: OR = 1.50 (CI 0.67 – 3.36) *≥ 964 µg/m^3-y (N=50/154)*: OR = 1.75 (CI 0.77 – 3.97) *p* for trend = 0.083 **No lag, underground workers** *0 – 298 µg/m^3-y (N=29/81)*: OR = 1.00 (reference) *298 – 675 µg/m^3-y (N=29/63)*: OR = 1.45 (CI 0.68 – 3.11) *675 – 1465 µg/m^3-y (N=29/57)*: OR = 1.81 (CI 0.8 – 3.89) *≥ 1465 µg/m^3-y (N=29/63)*: OR = 1.93 (CI 0.90 – 4.15) *p* for trend = 0.123 **15-year lag, all workers** *0 – 3 µg/m^3-y (N=49/158)*: OR = 1.00 (reference) *3 – 72 µg/m^3-y (N=50/228)*: OR = 0.74 (CI 0.40 – 1.38) *72 – 536 µg/m^3-y (N=49/157)*: OR = 1.54 (CI 0.74 – 3.20) *≥ 536 µg/m^3-y (N=50/123)*: OR = 2.83 (CI 1.28 – 6.26) *p* for trend = 0.001 **15-year lag, underground workers** *0 – 81 µg/m^3-y (N=29/92)*: OR = 1.00 (reference) *81 – 325 µg/m^3-y (N=29/52)*: OR = 1.18 (CI 0.52 – 2.68) *325 – 878 µg/m^3-y (N=29/69)*: OR = 0.84 (CI 0.39 – 1.82) *≥ 878 µg/m^3-y (N=29/51)*: OR = 2.08 (CI 1.01 – 4.27) *p* for trend = 0.062

		≥ 1,803 µg/m³-m (N=256): HR^U = 1.12 (CI 0.83 – 1.52) HR^A = 1.36 (CI 0.98 – 1.89) *p* for $trend^U$ = 0.97 *p* for $trend^A$ = 0.39 **5-year lag, without mechanics** *< 371 µg/m³-m (*N=122): HR^U = 1.00 (reference) HR^A = 1.00 (reference) *371 - 860 µg/m³-m (N=191):* HR^U = 1.18 (CI 0.92 – 1.52) HR^A = 1.31 (CI 1.01 – 1.71) *860 - 1,803 µg/m³-m (N=202):* HR^U = 1.17 (CI 0.88 – 1.55) HR^A = 1.38 (CI 1.02 – 1.87) *≥ 1,803 µg/m³-m (N=226):* HR^U = 1.19 (CI 0.86 – 1.63) HR^A = 1.48 (CI 1.05 – 2.10) *p* for $trend^U$ = 0.61 *p* for $trend^A$ = 0.16 **10-year lag, all workers** *< 167 µg/m³-m (*N=114): HR^U = 1.00 (reference) HR^A = 1.00 (reference) *167 – 596 µg/m³-m (N=183):* HR^U = 1.04 (CI 0.79 – 1.37) HR^A = 1.14 (CI 0.86 – 1.52) *596 – 1,436 µg/m³-m (N=205):* HR^U = 1.01 (CI 0.74 – 1.37) HR^A = 1.18 (CI 0.85 – 1.64) *≥ 1,436 µg/m³-m (N=277):* HR^U = 1.03 (CI 0.72 – 1.45) HR^A = 1.25 (CI 0.86 – 1.82) *p* for $trend^U$ = 0.96 *p* for $trend^A$ = 0.39 **10-year lag, without mechanics** *< 167 µg/m³-m (*N=112): HR^U = 1.00 (reference) HR^A = 1.00 (reference) *167 – 596 µg/m³-m (N=179):* HR^U = 1.06 (CI 0.80 – 1.40) HR^A = 1.17 (CI 0.88 – 1.57)	

		596 – 1,436 µg/m^3-m (N=202): HR^U = 1.05 (CI 0.77 – 1.45) HR^A = 1.26 (CI 0.90 – 1.78) *≥ 1,436 µg/m^3-m (N=248):* HR^U = 1.12 (CI 0.78 – 1.61) HR^A = 1.41 (CI 0.95 – 2.11) *p* for trend^U = 0.57 *p* for trend^A = 0.15	
Duration of exposure	OR, Odds ratio CI, 95% confidence interval N = cases/controls Source: Steenland et al. 1990 **No cut-off date** *Long-haul driver* 1-21 years (N=205/218) OR = 1.25 (CI 0.78 - 1.97) 22-27 years (N=199/195) OR = 1.12 (CI 0.72 – 1.77) > 28 years (N=199/195) OR = 1.47 (CI 0.94 – 2.31) *Short-haul driver* 1-21 years (N=52/52) OR = 1.52 (CI 0.86 – 2.71) 22-27 years (N=40/34) OR = 1.73 (CI 0.92 – 3.25) > 28 years (N=29/57) OR = 0.83 (CI 0.45 – 1.56) *Truck mechanic* 1-21 years (N=22/13) OR = 2.23 (CI 0.97 – 5.17) 22-27 years (N=17/17) OR = 1.20 (CI 0.53 – 2.72) > 28 years (N=11/8) OR = 1.88 (CI 0.66 – 5.35) **Exposure after 1959** *Long-haul driver* 1-11 years (N= 162/230) OR = 1.08 (CI 0.68 – 1.70) 12-17 years (N= 228-203) OR = 1.41 (0.90 – 2.21) > 18 years (N= 213-171) OR = 1.55 (CI 0.97 – 2.47 *p* for trend = 0.04 *Short-haul driver*	No data	OR, Odds ratio CI, 95% confidence interval N = cases/controls **All workers** *Unexposed (N=48/165):* OR = 1.00 (reference) *0 – 5 years (N=51/169)*: OR = 1.16 (CI 0.53 – 2.55) *5 – 10 years (N=20/95)*: OR = 0.88 (CI 0.38 – 2.03) *10 – 15 years (N=31/107)*: OR = 0.93 (CI 0.39 – 2.21) *≥ 15 years (N=48/130)*: OR = 2.09 (CI 0.89 – 4.90) *p* for trend = 0.043 **Underground workers** *0 – 5 years (N=37/92)*: OR = 1.00 (reference) *5 – 10 years (N=14/39)*: OR = 1.18 (CI 0.52 – 2.68) *10 – 15 years (N=25/60)*: OR = 0.84 (CI 0.39 – 1.82) *≥ 15 years (N=40/73)*: OR = 2.08 (CI 1.01 – 4.27) *p* for trend = 0.062

	1-11 years (N= 36-58) OR = 1.11 (CI 0.61 – 2.03) 12-17 years (N= 37-45) OR = 1.15 (CI 0.63 – 2.43) > 18 years (N= 40-31) OR = 1.79 (CI 0.94 – 3.42) *Truck mechanic* 1-11 years (N= 19-16) OR = 1.83 (CI 0.80 – 4.19) 12-17 years (N= 15-8) OR = 2.08 (CI 0.80 – 4.19) > 18 years (N=16-13) OR = 1.50 (CI 0.59 – 3.40)		
Lung cancer hazard / Excess lifetime risk of lung cancer death	Excess lifetime risk through age 75, assuming emission scenario in 1970, exposure beginning at age 20 and ending at the age 0f 64, unlagged model used (lagged model resulted in same outcomes) 45-year exposure at 5 µg EC/m^3: - 1.6 % (CI 0.4 – 3.1%) - 1.4 % (CI 0.3 – 2.7%) - 2.3 % (CI 0.5 – 4.6%) Assuming emissions in 1970 were 4.5 gm/mile, 7 gm/mile and 1.9 gm/mile, respectively	Lung cancer hazard per 1,000 µg/m^3-month (cumulative exposure) *No lag* Coefficient 0.0345 (SE 0.0349) RH = 1.04 (CI 0.97 – 1.11) *p* = 0.32 *5-year lag* Coefficient 0.0665 (SE 0.0379) RH = 1.07 (CI 0.99 – 1.15) *p* = 0.08 *10-year lag* Coefficient 0.0849 (SE 0.0501) RH = 1.09 (CI 0.99 – 1.20) *p* = 0.09 Adjusted for race, census region, calendar year of follow-up, duration of employment	No data
Notes as indicated by the authors			
General	Results depend on broad assumptions and are limited by a variety of factors		
Confounding: smoking habits		(1) analyses were adjusted for smoking habits (2) adjustment of smoking habits based on job title (is associated with socioeconomic status, which is associated with smoking habits) did not result in significant changes in RR (3) if short-term workers smoke more heavier than long-term	(1) limitations: data on smoking habits and other potential confounders were mainly derived from next-of-kin interviews; is a possibility of residual confounding (2) little is known about effect of the interaction between smoking an DEE exposure on lung cancer risk

		workers this could contribute to negative confounding when the results are not adjusted for duration of employment; to keep a commercial drivers license, drivers need to undergo medical examinations, which may select more healthier drivers that continue to work	(3) risk of lung cancer among mining workers was statistically significantly associated with smoking status and intensity (4) OR never smokers with DEE exposure (15-year lag): < 8 µg EC/m^3-yrs: OR = 1.0 8 – 304 EC/m^3-yrs: OR = 1.47 > 304 EC/m^3-yrs: OR = 7.30 -(5) OR overall study population, including 29% smokers, with DEE exposure (15-year lag): < 8 µg EC/m^3-yrs: OR = 1.0 8 – 304 EC/m^3-yrs: OR = 1.12 > 304 EC/m^3-yrs: OR = 2.40 (6) proportion smokers in study was substantially lower than in general population (29% versus 51%)
Precision of (past) exposure and emission levels	(1) exposure data extracted from a sample of measurements in 1990; no data on actual exposure (2) assumption is made that extrapolation over time is proportional to vehicle miles traveled by heavy trucks, and to the level of emissions of particulates from heavy duty engines; they appear to be reasonable, but how accurate these are is unknown; evaluation of assumption is not possible due to a lack of data on actual highway levels of EC, or particulate matter over time (3) it is unknown to what degree drivers may have been exposed to EC from their own truck; however, if assumption parameter is changed no significant variability in results is found (4) data on past emission is sparse, therefore three different emission scenarios were modeled (best estimate, lowest and highest estimate of emission levels); exposure coefficients remained in relatively narrow range (0.0002 to 0.0008), with ELRs ranging from 1,4% to 2.3% (45 years of exposure, 5 µg EC/m^3)	(1) average exposure levels is unlikely to be an accurate surrogate for cumulative exposure levels, and pulmonary dose of particulates over time, because in this study average exposure was not significantly associated with lung cancer mortality risk (2) Assessment of the source of EC mass $PM_{1.0}$ revealed that ≥ 80% originated from DEE (3) estimates of past exposure are based on current exposure assessments at relevant work locations; in Steenland it is based on miles travelled and emission rates; in others also on fuel efficiency factors (4) there is a lack of exposure information before employments in one of the four companies; workers may have had up to 10 additional years of exposure in the trucking industry; this may underestimate the results	(1) estimates of DEE exposure had some imprecision, which is most likely due to misclassification of exposure; true associations of lung cancer risk with DEE exposure may be higher than reported in this study

Estimation OR or RR		(1) RR decreased with duration of exposure; this was probably due to the healthy-worker effect and/or prevalent hires	(1) continuous models suggest steep slope at the low end of exposure-response curve, and a levelling (or perhaps even a decline) at the higher end of the curve; explanation include a) biological saturation of metabolic activation, enhanced detoxification, an/or greater DNA repair efficiency at higher exposure levels, and/or b) greater misclassification of DEE exposure at higher exposure levels
Evaluation by others	**Steenland et al. 1998**	**Garshick et al. 2012**	**Silverman et al. 2012**
HEI report (2015)		*Overall view* Well-designed and well-conducted; progress made on addressing number of major limitations that had been identified in previous epidemiological studies; data can be usefully applied in quantitative risk assessment; uncertainties in study should be considered in deriving an exposure-response relationship *Strengths of the study* (1) appropriate metric for DEE exposure used (2) retrospective exposure assessment is conceptually and statistically sound (3) investigators were able to validate some components of their exposure model (4) study included sensitivity analyses to cope with alternative assumptions (5) the study was the largest of his kind in the USA (6) appropriate use of Cox proportional hazards regression models *Limitations* (1) difficult to reconstruct historical exposure to SEC (is a general feature in retrospective research). Due to limited availability of data some assumptions had to be made (2) No adjustments are made for smoking habits, due to a	*Overall view* Well-designed and well-conducted; progress made on addressing number of major limitations that had been identified in previous epidemiological studies; data can be usefully applied in quantitative risk assessment; uncertainties in study should be considered in deriving an exposure-response relationship *Strengths of the study* (1) retrospective exposure assessment was logically constructed, and incorporated state-of-the-art methods (2) process of designing study met high standards of scientific research (3) sufficient statistical power and relevant data on covariates (4) includes strategy for collecting data on controlling potential exposure to other carcinogenic substances, such as radon, asbestos, silica, PAHs, and smoking habits (5) high quality of ascertainment health outcomes (6) appropriate use of estimation methods and models, such as Cox proportional hazards modeling (7) study included sensitivity analyses to cope with alternative assumptions (8) all data are publicly available

		lack of data. Assumptions are based on job-level smoking data (3) adjustment method for healthy worker survivor bias by using duration of work is not a common method; this makes comparison with other studies, who did not adjust in such a way, difficult	*Limitations* (1) difficult to reconstruct historical exposure to SEC (is a general feature in retrospective research). Questions has raised about the validity of historical exposure assessment by choice of CO, horsepower, etc. (2) Combined work location and smoking variables made results more challenging to apply in quantitative risk assessments (3) high level of confidence that radon is not a major confounder in the study, and thus that adjustment for it is not necessary

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