Diesel Engine Exhaust

Health-based recommended occupational exposure limit

To: The State Secretary of Social Affairs and Employment
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Health Council of the Netherlands

contents

samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad voor de beroepsmatige blootstelling aan uitstoot (emissie) van dieselmotoren blootstellingconcentraties afgeleid ten behoeve van het vaststellen van een grenswaarde. De blootstellingsconcentraties komen overeen met vooraf vastgestelde risiconiveaus voor het overlijden aan longkanker bij beroepsmatige blootstelling aan dieselmotoremissie. Het gaat om de uitstoot van dieselmotoren die petroleumdiesel als brandstof gebruiken. De blootstellingsconcentratie die overeenkomt met het streefrisiconiveau is 0,011 microgram (µg) respirabele elementaire koolstofdeeltjes per kubieke meter (m^3) lucht. De blootstellingsconcentratie dat overeenkomt met het verbodsrisiconiveau is 1,03 µg/m^3. De gegevens waarvan de blootstellingsconcentraties zijn afgeleid zijn afkomstig van onderzoek onder werknemers die blootstonden aan emissie van dieselmotoren zonder systemen om de emissie te reduceren.

De Gezondheidsraad heeft een vaste rol bij de advisering over de bescherming van werknemers tegen mogelijke schadelijke effecten van stoffen waar zij tijdens hun werk mee in aanraking kunnen komen. Zo beoordeelt de Gezondheidsraad de toxische eigenschappen en gezondheidseffecten van deze stoffen en doet zij aanbevelingen voor gezondheidskundige advieswaarden. Deze aanbevelingen vormen de basis voor een door de overheid vast te stellen grenswaarde. Meer informatie over de rol van de Gezondheidsraad rondom gezonde arbeidsomstandigheden staat op www.gezondheidsraad.nl.

De aanbeveling is tot stand gekomen in de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) – een vaste commissie van de Gezondheidsraad. In samenwerking met de *Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals* (NEG) heeft de commissie eerder al de toxiciteit van dieselmotoremissie geëvalueerd, waarvan de resultaten in 2016 zijn gepubliceerd door de NEG. De evaluatie kan worden geraadpleegd op de website van de Gezondheidsraad. De commissie heeft zich in dit advies gebaseerd op de evaluatie van 2016.

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

Gezondheidsrisico's

Dieselmotoremissie afkomstig van dieselmotoren die petroleumdiesel als brandstof gebruiken, bestaat uit een mengsel van 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 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). Voorbeelden van industrieën waar werknemers beroepsmatige blootgesteld kunnen worden aan dieselmotoremissie zijn de transportsector, bouwsector, de scheepvaart, landbouwsector, bosbouw, afvalverwerking en spoorwegen. Dieselmotoren zijn in allerlei maten en soorten verkrijgbaar, afhankelijk van het gewenste gebruik. Ook zijn er verschillen in de mate waarin emissiereductiesystemen zijn toegepast. Deze systemen verminderen onder meer de uitstoot van roetdeeltjes, waardoor de samenstelling (en dus de blootstelling) van de emissie anders is dan de samenstelling van de emissie van dieselmotoren die niet of onvoldoende voorzien zijn van zo'n systeem.

Longkanker uitgangspunt voor het afleiden van op risico gebaseerde blootstellingsniveaus

De commissie heeft ervoor gekozen om op risico gebaseerde blootstellingsconcentraties af te leiden, omdat blootstelling aan dieselmotoremissie tot kanker kan leiden, in het bijzonder de blootstelling aan de roetdeeltjes in de emissie.

Dieselmotoremissie bevat kankerverwekkende stoffen die het genetisch materiaal (DNA) in cellen kunnen beschadigen. Voor dit type stoffen is geen blootstellingsconcentratie aan te geven waaronder geen kanker meer optreedt en verondersteld wordt dat er bij elke blootstelling, hoe laag ook, een bepaalde kans bestaat op het ontstaan van kanker. In dit geval is de aanpak gericht op het beperken van het kankerrisico. De minister van SZW heeft vooraf twee risico-niveaus vastgesteld: een streefrisiconiveau en een verbodsrisiconiveau. Het streven is niet meer dan 4 extra gevallen door kanker als gevolg van beroepsmatige blootstelling, bovenop het aantal gevallen per 100.000 sterfgevallen in de algemene bevolking. Het verbodsrisiconiveau is 4 extra bovenop het aantal per 1.000. Als bijvoorbeeld van elke 100.000 mannen die in Nederland overlijden er 34.000 overlijden aan kanker, zou 40 jaar beroepsmatige blootstelling volgens het streefrisiconiveau niet mogen leiden tot meer dan 34.004 (4 plus 34.000) sterfgevallen door kanker per 100.000 sterfgevallen. Het verbodsrisiconiveau houdt in dat geval in: niet meer dan 344 (4 plus 340) sterfgevallen door kanker per 1.000 sterfgevallen. De commissie schat bij welke luchtconcentraties het risico op longkanker uitkomen op deze twee risico-niveaus.

Drie grote epidemiologische onderzoeken gebruikt

De commissie leidt blootstellingsconcentraties bij voorkeur af 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, waarbij de werknemers in het verleden zijn blootgesteld aan dieselmotoren met uitstoot aan roetdeeltjes. In deze onderzoeken is gekeken naar de relatie tussen longkankersterfte en kwantitatieve blootstelling aan emissie van dieselmotoren. Voor blaaskanker zijn dergelijke onderzoeken niet beschikbaar. De commissie is daarom uitgegaan van de onderzoeken naar longkanker. De resultaten van de onderzoeken zijn mogelijk beïnvloed door onzekerheden in de schattingen van de blootstellingsniveaus in het verleden, roken en gelijktijdige blootstelling aan kankerverwekkende stoffen afkomstig van andere bronnen op het werk dan van dieselmotoren. Volgens de commissie zijn de onderzoekers voldoende zorgvuldig met die onzekerheden omgegaan, zodat de commissie de onderzoeken geschikt vindt voor het afleiden van de blootstellingsconcentraties.

Respirabele elementaire koolstofdeeltjes als blootstellingsparameter

In de drie onderzoeken is de blootstelling aan dieselmotoremissie uitgedrukt in respirabele elementaire koolstofdeeltjes. Dit is volgens de commissie de beste blootstellingsmarker voor dieselmotoremissie. Elementair koolstof is een specifieke en gevoelige indicator voor blootstelling aan roetdeeltjes uit dieselmotoremissie, hoewel het niet zelf kanker veroorzaakt. Elementair koolstof is geschikt als indicator omdat het goed te meten is en een nauwkeurige weergave geeft van de concentratie (roet)deeltjes in de emissie. Daarnaast zijn dieselmotoren op de meeste werkplekken de enige bron van emissie van elementair koolstof en kan door specifieke bemonstering onderscheid worden gemaakt tussen elementair koolstof afkomstig van verschillende bronnen.

Gegevens over dieselmotoren zonder emissiereductiesystemen

De drie onderzoeken zijn uitgevoerd onder werknemers die blootstonden aan dieselmotoren zonder emissiereductiesystemen. In de periode 2006 - 2013 werden strengere Europese normen ingesteld om de emissie van dieselmotoren terug te dringen en de atmosferische luchtvervuiling te verminderen. Deze emissienormen gelden voor nieuwe dieselmotoren. Het zal echter nog jaren duren voordat alle langer bestaande dieselmotoren voor transport en stroomvoorzieningen vervangen zullen zijn door motoren die voldoen aan de huidige emissienormen. Bij de evaluatie van de NEG en de commissie zijn daarom alle gegevens geëvalueerd, inclusief de gegevens bij blootstelling aan emissie van dieselmotoren zonder noemenswaardige emissiereductiesystemen. Er zijn op dit moment onvoldoende wetenschappelijke gegevens om te kunnen kwantificeren in welke mate

toepassing van de nieuwste emissiereductiesystemen het risico op kanker door langdurige beroepsmatige blootstelling aan dieselmotoremissie vermindert of andere nadelige gezondheidseffecten voorkomt.

Meta-analyse

De commissie heeft voor het afleiden van de blootstellingsconcentraties gebruik gemaakt van een meta-analyse, waarin de drie onderzoeken zijn samengevoegd. Door het samenvoegen van verschillende onderzoeken (een meta-analyse) kan een meer betrouwbare uitkomst worden verkregen. Op basis van de meta-analyse analyse schat de commissie dat de concentraties van respiratoire elementaire koolstofdeeltjes in de lucht, die samenhangen met 4 extra sterfgevallen door longkanker bij 40 jaar aan beroepsmatige blootstelling aan dieselmotoremissie, per 100.000 en 1.000 sterfgevallen, gelijk zijn aan respectievelijk 0,011 µg/m^3 en 1,03 µg/m^3. De concentraties betreffen 8-urige tijdgewogen gemiddelde concentraties.

Advies aan de minister

Naar schatting van de commissie is de luchtconcentratie aan respirabele elementaire koolstofdeeltjes, die als maat fungeren voor de blootstelling aan de uitstoot van roetdeeltjes van dieselmotoren met een petroleumbasis als brandstof, als volgt.

- Bij 4 extra gevallen van sterfte aan longkanker door 40 jaar beroepsmatige blootstelling per 100.000 sterfgevallen (streefrisiconiveau), is de concentratie gelijk aan 0,011 µg/m^3.
- Bij 4 extra gevallen van sterfte aan longkanker door 40 jaar beroepsmatige blootstelling per 1.000 sterfgevallen (verbodsrisiconiveau), is de concentratie gelijk aan 1,03 µg/m^3;

De concentraties zijn tijdgewogen gemiddelde concentraties over een 8-urige werkdag.

Executive summary

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands has derived occupational exposure concentrations to diesel engine emissions (DEE) that correspond to predetermined (target and prohibition) risk levels for death from lung cancer due to occupational exposure to diesel engine emissions. It concerns the emission of diesel engines powered by petroleum-diesel fuels. The exposure concentrations are derived to set an occupational exposure limit by the Minister. The concentrations corresponding to the target risk level is 0.011 micrograms (µg) of respirable elemental carbon particles in DEE per cubic metre (m^3) of air. The exposure concentration corresponding to the prohibition risk level is 1.03 µg/m^3. The data from which these exposure concentrations were estimated are obtained from studies in workers who had been exposed to emissions from diesel engines with no effective emission reduction systems.

The Health Council has a permanent role in giving scientific advice to help protecting workers against the potentially harmful effects of any substances that they may encounter in the course of their work. In this connection, the Health Council assesses the toxic properties and health effects of these substances, and makes recommendations for health-based occupational exposure limits. These recommendations form the basis for an legally-binding occupational exposure limit to be set by the government. Further details concerning the Health Council's role with regard to healthy working conditions can be found at www.gezondheidsraad.nl.

The recommendations were formulated by the Dutch Expert Committee on Occupational Safety (DECOS) – a permanent committee of the Health Council. The Committee has evaluated the toxicity of diesel engine emissions on a previous occasion, in collaboration with the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). That evaluation, which was published by the NEG in 2016, can be viewed at the Health Council website. The Committee has based its recommendations in the current advisory report on that 2016 evaluation.

Diesel engine emissions pose a wide range of health risks to a wide range of workers

Health risks

Emissions from diesel engines powered by petroleum-diesel fuels consist of various gases and particles, which are produced by the combustion of diesel fuel in the engine. Such emissions contain substances that, when inhaled, are harmful to health. Their potential health effects are inflammatory reactions in the lungs, disorders of the heart and blood vessels, allergic disorders, aggravated symptoms of asthma, and various types of cancer – especially lung cancer and bladder cancer.

Exposure in the workplace

Throughout the world, diesel engines are used for transport (powering trucks, trains, ships, buses, tractors, and cars) and in the power industry (compressors, pumps and small generators). Workers can be subjected to occupational exposure to diesel engine emissions in industries such as the transport sector, the construction sector, shipping, agriculture, forestry, waste treatment, and railways.

Diesel engines are available in various sizes and types, depending on their intended use. They also differ in the extent to which emission reduction systems are used. One function of these systems is to reduce the emission of soot particles. As a result, the composition of the actual emission (and, thus, the exposure involved) differs from that of diesel engines that are equipped with inadequate emission reduction systems, or none at all.

Lung cancer as the starting point for deriving risk-based exposure levels

The Committee has chosen to derive risk-based exposure levels, because exposure to diesel engine emissions – especially exposure to the soot particles in such emissions – can lead to cancer.

Diesel engine emissions contain carcinogenic substances that can damage cells' genetic material (DNA). In the case of substances like this, it is not possible to identify an exposure level at which no cancer at all occurs. Thus, it is assumed that every level of exposure, however low, involves a certain risk of developing cancer. In this case, the approach focuses on limiting the cancer risk involved. The Minister of Social Affairs and Employment has established two risk levels in advance: a target risk level and a prohibition risk level. In terms of cancer due to occupational exposure over a 40-year period, these risk levels correspond to four additional cancer cases, which are added to the number of cancer death cases per 100,000 and per 1,000 overall death cases in the general population, respectively. By way of illustration, in the Netherlands, if every 100,000 men who die 34,000 died from cancer, the target risk level corresponds to 34,004 (4 plus 34,000) deaths due to cancer per 100,000 overall deaths. The prohibition level would then be no more than 344 (4 plus 340) death cases of cancer per 1,000 overall deaths. The Committee estimates at which exposure concentrations the risk of cancer correspond to the target and prohibition risks levels.

Three large epidemiological studies used

The Committee's preferred approach is based on epidemiological studies. It has identified three large-scale cohort studies that are suitable for this purpose. One of these studies focuses on miners, and the other two involve transport company workers. All of these subjects were, in the past, exposed to diesel engines that emitted

soot particles. These studies explored the relationship between lung cancer mortality and quantitative exposure to diesel engine emissions. No such studies have been published with regard to bladder cancer. Accordingly, the Committee has focused on the lung cancer studies. In the cancer studies, uncertainties on actual historical exposure levels, smoking or co-exposure to known carcinogenic substances from other sources than diesel engines, may have influenced the outcome. However, according to the DECOS, these uncertainties are sufficiently accurate addressed, and, therefore, the DECOS considers the data from the studies suitable to derive risk-based occupational exposure levels.

Respirable elemental carbon particles as exposure parameter

In all three studies, exposure to diesel engine emissions was expressed in terms of respirable elemental carbon particles. According to the Committee, this is the best exposure marker for diesel engine emissions. Although it does not itself cause cancer, elemental carbon is a specific and sensitive indicator of exposure to soot particles from diesel engine emissions. Its suitability as an indicator derives from the fact that it is easy to measure and that it gives an accurate representation of the concentration of particles (including soot particles) in the emission. Furthermore, in most workplaces, diesel engines are the only source of elementary carbon emissions. Accordingly, specific sampling can be used to differentiate between elemental carbon from different sources.

Data on diesel engines with no effective emission reduction systems

The three studies were performed on workers who had been exposed to diesel engines with no effective emission reduction systems. Between 2006 and 2013, stricter European standards were introduced to cut diesel engine emissions, with the aim of reducing atmospheric air pollution. These emission standards apply to new diesel engines. It will, however, be many years before all of the diesel engines now being used for transport and in the power industry have been replaced by engines that meet current emission standards. For this reason, the evaluations conducted by the NEG and the Committee examined every single item of data, including data on exposure to the emissions of diesel engines with no effective emission reduction systems. As yet, there is insufficient scientific data to quantify the efficacy of the latest emission reduction systems, in terms of mitigating or eliminating the risk of cancer or of other adverse health effects incurred by long-term occupational exposure to diesel engine emissions.

Meta-analysis

The Committee derived risk-based exposure levels by using a meta-analysis that combined these three studies. If a number of studies are combined (a meta-analysis), this can deliver a more reliable outcome. Based on the meta-analysis, the Committee estimated that the concentrations of respirable elemental carbon from DEE, which correspond to 4 extra cases of

lung cancer death due to 40 years of occupational exposure to DEE, per 100,000 and 1,000 death cases, equals to 0.011 µg/m^3 and 1.03 µg/m^3, respectively. The exposure levels are 8-hour time-weighted average concentrations.

Advice to the minister

The Committee estimates that the exposure concentrations of respirable elemental carbon in the air, which serve as parameter for exposure to diesel engine exhaust powered by petroleum-diesel fuels, and which corresponds to:

- 4 extra death cases of lung cancer per 100,000 (target risk level), for 40 years of occupational exposure, equals to 0.011 µg REC/m^3,
- 4 extra death cases of lung cancer per 1,000 (prohibition risk level), for 40 years of occupational exposure, equals to 1.03 µg REC/m^3.

The exposure levels are 8-hour time-weighted average concentrations.

01 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. The purpose of these evaluations is to recommend health-based occupational exposure limits (HBR-OELs) 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 (DEE). It concerns the exhaust of diesel engines powered by petroleum-diesel fuels. The 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 evaluation was published by the Swedish National Institute of Occupational Health (in the *Arbete och Hälsa* criteria documentation series). It is available on the website of the Health Council.[1]

1.2 Committees and procedure

The members of the DECOS and the consulted experts, are listed on the last page of this report.

In 2017, the president of the Health Council released a draft of this advisory report for public review. The comments received have been taken into account by the committee in deciding on the final recommendation of the advisory report. The comments, and the reply by the Committee, can be found 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 criteria documentation report.[1] The documentation report is partly based on IARCs' evaluation (2014).[2] In addition, the DECOS retrieved new scientific data from PubMed and Toxline (from June 2015 up to January 2019).

02 substance identification

The description below is based on Chapter 2 of the NEG-DECOS criteria documentation.[1] The documentation can be found on the website of the Health Council.

Diesel engines are widely used for transport and power supply, and are dominating power-sources for heavy-duty vehicles and engines. The working population may be exposed to DEE emitted by: on-road vehicles (e.g., passenger cars, buses, trucks, vans), off-road vehicles (e.g., forklift trucks, tractors, harvesting machines, excavators, military vehicles), sea-going and inland water vessels, locomotives, and stationary equipments (e.g., compressors, pumps, electricity generators, cranes and other machinery).

DEE from engines powered by petroleum-diesel fuels is a complex mixture of gaseous and particulate phases, produced during the combustion of diesel fuels. The emission rate and exact composition of the exhaust depends on type, age, operational condition, and maintenance of the engine. Also the composition and physical properties of the diesel fuels, and the exhaust after treatment techniques applied, determine the emission and composition of the exhaust. 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. The particulate phase contains elemental carbon (EC), organic compounds, sulphates, nitrates, and metals and other trace elements. Due to incomplete combustion, in the emission well-known carcinogenic substances may be found, such as certain (nitro-)polycyclic aromatic hydrocarbons (PAH; e.g., benzo(a)pyrene, nitro- and dinitroarenes).

DEE is considered one of the sources of atmospheric air pollution, in particular traffic-related air pollution, causing adverse health effects in the general population. In the past two decades, in the European Union, the United States of America and elsewhere, regulations were set for *new* on- and non-road vehicles and engines, to lower the emission levels of diesel engine driven vehicles and equipment. The regulations have fostered an evolution of diesel engine and exhaust after-treatment technologies, resulting in lower emissions of diesel engine particles, lower emissions of organic compounds, such as PAH and aldehydes, and lower emission of gases, such as nitrogen oxides. Due to new technologies, also the typical composition of diesel exhaust changed, i.e. the proportion of EC decreased (from 75% to 13%), of organic carbon increased (from 19% to 30%), and of nitrogen dioxide increased from 10% to up to 50% of the nitrogen oxides. Consequently, exhaust composition of newer diesel engines with emission reduction systems differ from that of older diesel engines.

It will take many years before the older diesel engines are replaced by engines that meet the current emission regulations. Therefore, near future occupational exposure will be related to older diesel engine technology. For this reason, the NEG and the DECOS evaluated scientific data on the health risks to occupational exposure to DEE from all types of diesel engine driven vehicles and equipment, including engines before the introduction of new technologies[a] (see the NEG-DECOS criteria documentation).[1]

[a] In the scientific literature diesel engines are distinguished in terms of ‘old’, ‘traditional’, or ‘engines without implementation of new technology’ for referring to engines which were in use before the new technology diesel engines were introduced in the years after 2000.

03 workplace air monitoring

The description below is based on Chapter 4 of the NEG-DECOS criteria documentation.[1] The documentation can be found on the website of the Health Council.

Since DEE has a complex composition, varying indicators have been applied for the measurement of DEE exposure in workplaces. For the particulate phase of diesel engine exhaust, mainly respirable particulate mass (PM_{10}, $PM_{2.5}$ and $PM_{1.0}$), and EC have been measured. For the gas phase, NO_x and CO are generally applied as exposure indicators.[1]
The present advisory report focuses on respirable elemental carbon (REC) in the particulate phase of the diesel exhaust as exposure parameter, because of the association of diesel exhaust particulate matter with lung cancer risk (see Chapters 4 and 6). The DECOS emphasizes that there are no suggestions that elemental carbon is carcinogenic, but rather represents a marker of exposure to carcinogenic components in the particulate matter. Validated monitoring methods for measuring exposure to REC in workplaces are summarized below.

For measuring the particulate fraction of DEE, standardized gravimetric methods are available, such as the NIOSH method 5040.[3] Using this method, the respirable dust fraction is sampled, and analysed on the presence of REC. REC constitutes a large portion of the particulate mass in DEE, in particular from older diesel engines (≈ 75% of the DEP mass). The NIOSH method corrects for pyrolysis of organic carbon. In addition, a European standard reference method for measuring REC and organic carbon collected on (quartz fiber) filters is described by the NEN (Method 16909:2017)[4] Sampling in ambient air is done gravimetrically according to the NEN Method 12341:2014 for $PM_{2.5}$ mass concentration. EC from other sources, such as from coal dust or car tires, can be separated from DEE by size-selective sampling.[3-6]

04 adverse health effects

The description below is based on Chapter 9 and 10 of the NEG-DECOS criteria documentation.[1] The documentation can be found on the website of the Health Council.

4.1 Carcinogenicity

Observations in humans

At least thirty retrospective cohort studies and twenty case-control studies have been performed on lung cancer mortality and incidence among workers who had been mainly exposed to DEE (e.g., non-metal/potash miners, trucking industry workers, truck and bus drivers, transport maintenance workers, railroad workers, dock workers, heavy equipment workers). Most of these studies estimated exposure in a qualitative way by job title and years of work. In a few studies semi-quantitative and quantitative exposure levels in the past were estimated using job exposure matrices, current exposure levels (elemental or total carbon), or available emission data. Potential confounding in part of the studies included smoking habits, and exposure (in the past or present) to various other potential carcinogenic substances than the substances known to be present in DEE. Overall, these studies show an extensive evidence of an association between occupational exposure to DEE and lung cancer. Multiple case-control studies have been performed on occupational DEE exposure and bladder cancer. However, most of these studies showed serious shortcomings, such as not taking smoking habits into account, and low-quality of the exposure assessment. Overall, there is some evidence from case-control studies of an association between diesel engine exposure and bladder cancer, but this was not confirmed in cohort studies. In general, except for the lungs and the bladder, no consistent evidence has been found for cancers at other sites of the body. Evidence is hampered by limitations in exposure assessments, lack of adjustments for confounding, and the small number of cases.

The adverse associations were found in workers who had been exposed to DEE without the newest technologies to reduce or inhibit emission of particulate matter; no observational studies have been performed on the long-term health risks of workers exposed to DEE from new-technology engines.

Cancer burden in the working population

Cherrie et al. (2009) estimated that in 2004 in Great-Britain, 672 workers died of lung cancer due to occupational exposure to DEE particulates.[7] Brown et al. (2012) adds that in Great-Britain in 2004 DEE exposure occurred among 2 million workers.[8] They estimated that about 605 lung cancer deaths were attributable to occupational DEE exposure, which is in line with the estimations by Cherrie et al. In addition, Kim et al. (2018) estimated that in Canada in 2011 approximately 560 lung cancer incident cases and 460 lung cancer deaths were attributable to occupational DEE exposure (of a total population of 1.6 million workers with expected DEE exposure).[9] In addition, Vermeulen et al. (2014) estimated that 45 years of

occupational exposure to DEE at 1, 10 and 25 µg respirable elemental carbon (REC)/m^3 results in 17, 200 and 689 excess lung cancer deaths per 10,000 individuals, respectively, by the age of 80 years.[10]

Observations in animals

Mixed results are reported on animal carcinogenicity after long-term exposure to whole DEE or extracts of DEE (without particles removed). Several of the more than twenty studies reported statistically significantly increased lung tumour incidences in rats, which were exposed to whole DEE at concentrations of over 2,200 µg diesel engine particles (DEP)/m^3. No clear DEE-induced lung tumours were found in mice and hamsters. Tumours at other sites of the body were not reported. In an animal inhalation study, in which rats were exposed to whole DEE from new technology diesel engines (3-12 µg DEP/m^3 (≈ 1-3 µg REC/m^3), 0.2-8 mg NO_2/m^3), no tumours were found.

Genotoxicity

In vitro mutagenicity tests showed that whole DEE (without particles removed) or particulate matter extracts of DEE are mutagenic. In vivo genotoxic responses have been described in rodents inhaling DEE (DNA strand breaks, increased DNA adducts, oxidative DNA damage, and mutations in the lungs of transgenic mice). Also, in humans who were exposed to air containing whole DEE, increased DNA adducts, DNA damage and other genotoxic effects were observed. Limited data are available showing that also the gaseous phase of DEE may be mutagenic.

IARC classification

In 2014, IARC published an extensive evaluation on the carcinogenic and genotoxic potential of DEE.[2] IARC concluded that "*there is sufficient evidence in humans for the carcinogenicity of diesel engine exhaust*" and that "*diesel engine exhaust causes cancer of the lung*". Furthermore, IARC stated that "*a positive association has been observed between exposure to diesel engine exhaust and cancer of the urinary bladder*". IARC based its conclusion on studies in which workers were exposed in the past to exhaust from diesel engines, which were in use before systems or technologies were introduced to reduce emission of particles. In addition, concerning animal experiments, IARC concluded that "*there is sufficient evidence in experimental animals for the carcinogenicity of whole diesel exhaust*", and of "*diesel engine exhaust particular matter*" and "*extracts of diesel engine exhaust particles*". Inadequate evidence is available in experimental animals for the carcinogenicity of gas-phase DEE. Based on these findings IARC classified DEE in Group 1 "*carcinogenic to humans*".

4.2 Non-Carcinogenic effects

4.2.1 Observations in humans

Experimental studies (single exposure)

Nasal, throat and eye irritation is described in experiments with healthy human volunteers after a single exposure to inhaled DEE (concentrations of exhaust varying from 108 to 300 µg DEP/m^3 (≈ 81 to 225 µg EC/m^3), 0.2 to 1.9 ppm NO_2 (≈ 0.4-3.6 mg NO_2/m^3) and 0.04 to 0.4 mg formaldehyde/m^3), for two hours with or without doing light exercise (biking). The irritating properties of DEE could be explained by the presence of known irritating constituents in the gas phase of the exhaust, such as NO_2 and aldehydes. In addition, in healthy human volunteers, single exposure to DEE for two hours induced pulmonary effects (e.g., lung inflammation, lowered lung function). These effects were observed at exposure levels of the exhaust varying from 100 to 300 µg DEP/m^3 (≈ 75 to 225 µg EC/m^3), and 0.2 to 1.9 ppm NO_2 (≈ 0.4-3.6 mg NO_2/m^3), with or without doing light exercise (biking).

Furthermore, most experiments with healthy volunteers showed that inhalation of DEE (for 1-2 hours, with or without exercise) induces effects on haematological and cardiovascular effect parameters (e.g., changes in blood pressure, increased neutrophils and platelet counts in the blood), although in some studies no effects on these parameters were observed. The volunteers were exposed to DEE containing DEP, NO_2 and CO at concentrations varying from 100 to 350 µg DEP/m^3 (≈ 75 to 262 µg EC/m^3), 0.2 to 3.4 ppm NO_2 (≈ 0.4 to 6.5 mg NO_2/m^3), and 2.8 to 6.9 ppm CO (≈ 3.2 to 8.1 mg CO /m^3).

Limited data are available on neurological and immunological effect parameters, from which no clear conclusions can be derived.

Observational studies (long-term exposure)

A few cohort studies have been performed among (non-metal) miners, (tunnel) construction workers and farmers. Occupational exposure to DEE was associated with lung effects and ischemic heart diseases (e.g., lowered lung function, increased incidence and mortality from COPD, and increased mortality from ischemic heart disease). In some studies such effects were not observed, and in other studies exposure to dust from mining activities may have influenced the outcome. For instance, workers in a German salt mine showed a decline in lung function over a period of five years upon combined exposure to DEE and dust. Mean personal exposure levels were: 90 µg REC/m^3, 0.4-0.5 ppm NO_2 (≈ 0.8-1.0 mg NO_2/m^3), 1.4-1.7 ppm NO (≈ 1.8-2.1 mg NO /m^3), 7.1-13 mg/m^3 inhalable dust and 0.8-2.4 mg/m^3 respirable dust.

Support for the suggestion that DEE can be associated with adverse lung effects and (ischemic) heart diseases comes from population-based environmental studies on the health risks from ambient air pollution, in particular pollution caused by traffic emissions. Many of these studies found strong associations between long-term exposure to ambient air

pollution and increased risks to declined lung function, exacerbation of pre-existing respiratory conditions (COPD, asthma), and cardiovascular mortality in adults. It is not clarified yet what constituents in traffic-related air pollution are associated with the harmful effects (DEP, (ultra)fine particles and/or other constituents).

4.2.2 Observations in animals

Single and short-term exposure (up to 13 weeks)

No animal experiments have been performed on the irritation and sensitization effects of the gaseous constituents in DEE after single exposure. In different animal species (rats, mice, and occasionally guinea pigs), inhalation of DEE for up to 13 weeks caused pulmonary effects (inflammation, decreased lung clearance), haematological and cardiovascular effects, neurological effects (limited data), and immunological effects.

Long-term exposure (19 weeks up to 130 weeks)

Long-term inhalation of DEE resulted in respiratory and pulmonary effects, such as deceased lung function, hyperplasia in the respiratory tract, inflammation and fibrosis in the lungs, and in changes in haematological and cardiovascular effect parameters. In most animal experiments, a series of different exposure concentrations of the exhausts were applied, which ranged from hundreds to thousands mg DEP/m^3 and 0.1 to 6.9 ppm NO_2 (≈ 0.2-13.2 mg NO_2/m^3). The lowest exposure levels at which effects on the respiratory tract are described were reported to be around 10 to 12 µg DEP/m^3 (≈ 3 µg REC/m^3) and 0.2 ppm NO_2 (≈ 0.4 mg NO_2/m^3). Also, adverse neurological effects (two studies) and immunological effects (one study) have been described, but the number of studies is limited. In addition, some studies suggest that exposure to DEE (≥ 170-300 µg DEP/m^3) may affect fertility in male rats and mice.

05
existing guidelines, standards and evaluations

5.1 General population

No national or international specific guidelines or standards exist for preventing adverse health effects in the general population due to exposure to DEE. However, for the general population standards exist to control for ambient air pollution. A variety of natural and anthropogenic sources contribute to the ambient air pollution, including DEE from vehicles and stationary sources. Constituents found in polluted air, which are related to adverse health effects, are amongst others particulate matter, nitrogen oxides and carbon monoxide, substances which are also found in DEE. In the Netherlands and the European Union legally binding standards are set for particulate matter (PM_{10} and $PM_{2.5}$), nitrogen dioxide, carbon monoxide and many other substances that can be found in polluted air:[11]

Nitrogen dioxide	40 µg/m³, annual mean concentration 200 µg/m³, one-hour mean concentration
Carbon monoxide	10,000 µg/m³, 8-hour mean concentration
PM_{10}	40 µg/m³, annual mean concentration 200 µg/m³, one-hour mean concentration
$PM_{2.5}$	25 µg/m³, annual mean concentration
PAH	1 ng BaP/m³, annual mean concentration

In addition, the World Health Organization (WHO) assessed (health-based) standards to prevent adverse health effects of ambient air pollution. Regarding particulate matter, the WHO stated that "*small particulate matter has health impacts even at very low concentrations*" and that "*indeed no threshold has been identified below which no damage to health is observed*". In addition, "*$PM_{2.5}$ can penetrate the lung barrier and enter the blood system. Chronic exposure to particles contributes to the risk of developing cardiovascular and respiratory diseases, as well as of lung cancer*". According to the WHO, the standard of $PM_{2.5}$ of 10 µg/m³, "*could reduce pollution-related deaths, by around 15%*", but that at this concentration level the life expectancy is lower than it would otherwise be without human sources.[12]

Nitrog en dioxide	40 µg/m³, annual mean concentration 200 µg/m³, one-hour mean concentration
PM_{10}	20 µg/m³, annual mean concentration 50 µg/m³, 24-hour mean concentration
$PM_{2.5}$	10 µg/m³, annual mean concentration 25 µg/m³, 24-hour mean concentration

5.2 Working population

5.2.1 Occupational exposure limits

In Appendix 1 of the NEG-DECOS criteria documentation, a list of occupational exposure limits set in other countries is given.[1] In Table 1, new data are included.

Table 1. Exposure limits set for DEE

Country	Particles (respirable, µg/m³)	REC (µg/m³)	Total carbon (respirable µg/m³)	NO_2 (ppm)	CO (ppm)	Year of introduction, remarks
The Netherlands	-	-	-	-	-	-
EU (SCOEL)	-	-	-	-	-	2017
Austria	100 (8-h TWA) 400 (15-min TWA)	-	-	-	-	At least since 2011
	300 (8-h TWA) 1,200 (15-min TWA)	-	-	-	-	At least since 2011; for underground mining
Germany - AGS	-	50 (1-h TWA, AGW)	-	-	-	Since 2017; the AGW states the concentration of a substance below which acute or chronic adverse health effects are not generally expected. AGWs are based exclusively on available occupational medical experience and toxicological findings.
Sweden	-	-	-	1	20	Since 1990 (CO) and 2004 (NO_2); OEL for exhaust gas in general
Switzerland	-	100	-	-	-	At least since 2012
USA - ACGIH	-	-	-	-	-	-
USA - NIOSH	-	-	-	-	-	-
USA - MSHA	-	-	160 (8-h TWA)	-	-	Since 2008; for underground metal/nonmetal mining
USA - OSHA	-	-	-	5 (ceiling)	50	PELs for individual components (not related in particular to DEE)

ACGIH, American Conference of Governmental Industrial Hygienists; AGS, Ausschuss für Gefahrstoffe; AGW, Arbeitsplatzgrenzwert; MSHA, Mine Safety and Health Administration; OSHA, Occupational Safety and Health Administration; PEL, Permissible Exposure Limit; SCOEL, Scientific Committee on Occupational Exposure Limits (European Union); TWA, time-weighted average concentration.

In the European Union and in Germany, the occupational exposure limits are based on a health-based scientific evaluation. In other countries no health-based evaluations have been performed in assessing legally binding occupational exposure limits for DEE.

The European Union

In 2017 a summary opinion on DEE was published by the European Commission advisory board, the Scientific Committee on Occupational Exposure Limits (SCOEL).[13] No recommendation for a health-based occupational exposure limit for traditional or new technology DEE was given. Regarding the traditional DEE, the SCOEL concluded that there is evidence of a direct genotoxic activity as well as for indirect genotoxicity. Therefore, it concluded that traditional DEE could be classified as a category B ("*genotoxic carcinogen, for which the existence of a threshold cannot be sufficiently supported*") or C ("*genotoxic carcinogen for which a practical threshold is supported"*) carcinogen. It also stated that "*Toxicological and pathobiological information from animal studies supports a mode of action, for which possibly a threshold could be established. However, the epidemiological evidence does not allow to identify a critical threshold that could serve for derivation of an OEL, and*

direct genotoxicity cannot be excluded". The SCOEL announced that further scientific technical analysis shall follow upon this issue.

Germany

In 2017, the federal Ausschuss für Gefahrstoffe (AGS) derived an occupational exposure limit for DEE of 50 µg EC/m^3 (8-h TWA).[14] It concerns exhaust from diesel engines without implementation of new technology for limiting emissions of in particular particulate matter. A main discussion was whether DEE could be considered as a direct acting genotoxic substance or not, and thus whether a threshold-based OEL could be established. Diesel engine particles consist of nuclei of EC, to which other substance could be absorbed, such as polycyclic aromatic hydrocarbons (e.g., benzo(a)pyrene and nitro-PAH). These substances are known genotoxic carcinogens. According to the AGS, these carcinogenic substances are in such low concentrations absorbed to the EC that it is not necessary to assess a non-threshold-based OEL. In addition, the fact that in animal experiments lung tumours were observed after exposure to particulate matter is explained by inflammation (chronic irritation). Thus, the AGS considered irritation and lung inflammation the critical effect against which workers should be protected. By preventing pulmonary inflammation, also tumour development will be prevented. In general, a threshold level exists below which no irritation is expected to occur. Experiments with humans on single exposure to DEE were not considered useful, since the increase in inflammatory parameters were related with the NO_2 in the exhaust. Furthermore, the AGS judged that findings of epidemiological studies were controversial and did not have sufficient quality to be used for quantitative risk assessment. For these reasons, the AGS derived a threshold-based OEL from data on chronic animal experiments. The AGS also gives suggestions for risk-based limit values (e.g., acceptable (4:100,000) and tolerable risks (4:1,000)) for the carcinogenic effects. Based on the animal experiments, it suggests an acceptable risk concentration level of 20 µg EC/m^3, which is a factor 2.5 lower than the recommended exposure limit.

5.2.2 Biological limit values

No legally binding standards set.

5.2.3 Skin and sensitization notation

No notation set.

06 hazard assessment

6.1 Health risks

The adverse health effects caused by exposure to DEE were evaluated in the NEG-DECOS criteria documentation.[1]

In summary, occupational exposure to DEE from engines powered by petroleum-diesel fuels, is associated with respiratory inflammation and adverse cardiovascular effects. It is also suggested that exposure may exacerbate respiratory disorders, such as asthma, and allergic diseases. Although the available data are limited and mainly based on animal experiments or studies in the general population, there is some evidence of adverse neurophysiologic symptoms, immunologic effects, and reproductive and developmental effects.

There is extensive epidemiological evidence of a relationship between occupational exposure to DEE from engines powered by petroleum-diesel fuels and lung cancer (see Chapter 9 and 10 of the NEG-DECOS criteria documentation). In short, most studies focused on lung cancer in combination with job title or with years of work. The majority of these studies found significant positive associations between DEE exposure and increased risk of lung cancer mortality, with risk ratios generally between 1.3 and 1.6. Higher risks ratios were found in some studies among the highest exposure groups. There is evidence pointing to an association between DEE exposure and bladder cancer. Increased risk of bladder cancer was noted in some case-control studies, but not in cohort studies. A number of the studies on bladder cancer had methodological shortcomings in exposure assessment, or did not take confounding factors sufficiently into account.

There is strong mechanistic evidence regarding the carcinogenic potential of DEE that whole DEE (without particles removed), organic extracts of DEE, and many individual components present in the particulate matter of DEE, have genotoxic properties. Tests of whole DEE extracts have shown that they induce DNA damage, gene and chromosomal mutations, changes in relevant gene expression, the production of reactive oxygen species and inflammatory responses.[2] Next to the genotoxic properties, the co-carcinogenic, cell-proliferative and/or tumour-promoting mechanisms probably contribute to the carcinogenicity. Limited data are available suggesting that the gaseous phase of DEE is carcinogenic and genotoxic.

Based on the available data on carcinogenicity, in 2014 the IARC concluded that there is sufficient evidence in human and animal experiments that DEE is carcinogenic to humans (Group 1).[2] DEE is also classified as carcinogenic to humans in the Netherlands.

Overall, the DECOS concludes that exposure to DEE can induce lung cancer, and that certain components present in the particulate matter of DEE induce lung cancer by a stochastic genotoxic mode of action. If a substance acts by a stochastic genotoxic mechanism, there is no threshold level below which it may reasonably be expected that there is no risk of adverse health effects. This is irrespective of the data indicating

that these or other components in DEE may also induce cancer by non-genotoxic mechanisms, thereby suggesting a threshold level below which no relevant adverse health effects occur. Thus, any exposure, no matter how low, involves a risk caused by the presence of genotoxic components. In situations such as this, the DECOS estimates Health-Based Calculated Occupational Cancer Risk Values (HBC-OCRVs). These values should not only protect against cancer, but also against all other adverse health effects.

6.2 Suitable carcinogenicity studies in deriving HBC-OCRVs

In deriving HBC-OCRVs, the DECOS prefers using data from epidemiological studies rather than animal experiments, because epidemiological data do not involve the uncertainties associated with the biological differences between animals and humans. Furthermore, the exposure conditions in epidemiological studies reflect real life exposure circumstances in an occupational setting. Data from animal experiments are considered only if epidemiological data are of insufficient quality or too limited.

Numerous cohort and case-control studies are available on lung (and bladder) cancer among workers exposed to DEE. However, only four studies included quantitative exposure-response data, which could be used to derive HBC-OCRVs (Steenland et al. 1998; Garshick et al. 2012; Silverman et al. 2012; and Möhner et al. 2013).[15-18] These include two nested case-control studies and two retrospective cohort studies on lung cancer mortality, in which DEE exposures (REC) are estimated retrospectively. Two studies were performed in the trucking industry and two in the mining industry. All four studies concerned exposure to DEE from engines powered with petroleum-diesel fuels, without the newest technologies to reduce emission of particulates.

A summary of the studies is described below. Study details are contained in Annex A.

Steenland et al. (1998) – Teamster trucking study

In 1998, Steenland et al. published the results of a quantitative exposure-response analysis using the data from a case-control study among workers in the US trucking industry (Central States Teamster Union).[15] Cases and controls (994 lung cancer deaths [based on death certificates], and 1,085 controls) were divided into 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 for long-haul drivers and leaks from trucks exhaust systems. Historical levels of exposure were linked to known work history. 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 status, diet and self-reported asbestos exposure. Also, cumulative exposure was modelled in lag times of 0 and 5 years, the latter excluding exposure occurring in the

last 5 years before lung cancer death. All analyses resulted in a significant positive trend for lung cancer risk with increasing cumulative exposure. The results of the analyses are shown in Annex A.

Garshick et al. (2012) – Truckers study

The second study among US trucking industry workers was a retrospective cohort study by Garshick et al.[18] Previous reports on the cohort study were published in 2007 by Laden et al. and in 2008 by Garshick et al.[30,31] Summarised, in total 31,135 work records were available of male workers employed in the US trucking industry in 1985. Lung cancer mortality was ascertained throughout 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.[32] 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 by proportional hazard regression analysis. Multiple exposure metrics were evaluated: time-dependent cumulative exposure modelled in lags of 0, 5 and 10 years, and time-dependent average exposure modelled in lags of 0 and 5 years. The full cohort was analysed, and a cohort excluding the mechanics. For mechanics, it was suggested that the validity of extrapolation of current exposure to historical estimates was invalid because of changing job duties. After adjusting for employment duration, Garshick et al. concluded that lung cancer mortality among truck drivers increased with increasing cumulative exposure to EC. The results of the analyses are shown in Annex A.

Silverman et al. (2012) – DEMS study

The nested case-control study by Silverman et al. is part of a large cohort mortality study of workers in the US non-metal mining industry,[17] which is described by Attfield et al. (2012).[33] Results of the cohort and nested case-control study on lung cancer mortality were consistent, both showing an exposure-response association. As the nested case-control study adjusted data for smoking habits, the DECOS has focused on this study. This Silverman 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 REC was conducted. Based on these measurements, location (ever underground or surface only) and job title, specific estimates were developed. Modelled historical trends in carbon monoxide levels, which were based on horsepower use and ventilation, were used for back extrapolation of REC measurements from 1998-2001 to estimate the historical annual average daily REC levels.[34] Logistic regression was used to assess the association between REC exposure and lung cancer mortality. The regression analysis was based on cumulative exposure modelled in a lag of 15 years. Silverman et al.

observed statistically significantly increasing trends in lung cancer risk with increasing cumulative and average REC exposure. The results of the analyses are shown in Annex A.

Möhner et al. (2013) – German potash mining study

This study was a reanalysis of the retrospective cohort study by Neumeyer-Gromen et al. (2009) among nearly 6,000 German potash miners, in which support was found for an association between cumulative exposure to DEE (total carbon) and lung cancer mortality.[41] In the reanalysis by Möhner et al. (2013), data on lung cancer mortality (a total of 68 cases and 304 controls) were used to study the influence of smoking status and previous occupational history on the DEE-induced lung cancer mortality risk etimates.[16] In regard to the latter, the authors considered employment periods before potash mining, with special interest for uranium mining. Information on smoking habits and occupational history before potash mining was gathered from medical records, and by linking to records from a nearby uranium company. Data on exposure measurements in 1991 on total carbon were used to design a job-exposure-matrix. The authors converted the exposure data to REC by using a correction factor. In the analyses cumulative exposure was modelled with a lag of 5 years. Without correcting for smoking status and former employment, no association was indicated between cumulative DEE-exposure and lung cancer risk (odds ratio 0.94 [95% confidence interval 0.64-1.38]). In addition, no association was found when data were corrected for smoking habits in combination with previous employment (odds ratio 1.04 [95% confidence interval 0.70-1.53]).[16] To the contrary, statistically significant positive associations were found between smoking and lung cancer mortality, and between former employment in the uranium mining industry and lung cancer mortality.

The authors noted the small number of cases and the wide confidence interval, suggesting a low precision of the point estimates for lung cancer. The results of the analyses are shown in Annex A. To the DECOS, it is not clear how exactly the authors adjusted the risk analysis on cumulative exposure for smoking combined with former employment. In addition, the DECOS noted the relative high percentage of missing data on smoking status and former employment. The DECOS adds that the reference group had a high mean cumulative exposure level (1st tertile < 983 µg REC/m^3-years; mean 624 µg REC/m^3-years) compared to almost all reference cumulative exposure levels in the other three studies.

Overall

Three of the four studies showed statistically significant positive associations and trends between cumulative REC exposure and lung cancer mortality in the trucking and mining industry, in which workers were mainly exposed to DEE (Steenland et al. 1998, Garshick et al. 2012, Silverman et al. 2012).[15,17,18] No association was found by Möhner et al. (2013).[16]

Quality of the studies for quantitative risk assessment

The methodological quality of the studies by Steenland et al. (1998), Silverman et al. (2012), and Garschik et al. (2012), and usefulness for quantitative risk analyses, are extensively discussed in the scientific literature, which has resulted in mixed opinions and conclusions.[19-25] The DECOS made use of the report by the independent diesel epidemiology panel from the Health Effects Institute (HEI, 2015), in which the studies by Garshick et al. (2012)[18] and Silverman et al. (2012)[17] were extensively reviewed to determine whether major limitations were correctly addressed, and whether the data presented in these two studies were of sufficient quality to be used in quantitative risk assessment.[26] The HEI panel included in its evaluation comments from published commentaries in the scientific literature, a public workshop, and an external peer-review of a draft of the report. It also performed additional investigations and analyses on the data presented in the two studies. Overall, the DECOS considers the HEI evaluation of high quality, and noted that the HEI evaluation covered the most important issues in the discussion. Earlier, in 1999, the HEI evaluated the quality of the exposure–response analysis by Steenland et al. (1998).[27] Also this evaluation was taken into account by the DECOS.

Overall, the main issues regarding the studies concerned bias due to uncertainties in the reconstruction of historical exposure levels, and confounding by the presence of other risk factors, such as smoking habits, and co-exposure to other potential carcinogenic substances. A summary is given below.

Estimation of historical exposure levels

In all studies, assumptions had to be made to estimate historical exposure levels, introducing some degree of uncertainty about actual historic exposure. Most of the studies used multiple occupational and environmental (emission) measurement sources, previous measurements from industrial hygiene surveys, and accounted for changes in engine development and use over time, to determine whether the historical exposure estimates were reasonable. To get an idea on the degree of uncertainty, Steenland et al. (1998) considered three different exposure scenarios (most plausible, the lowest exposure estimate, and the highest exposure estimate), which resulted in exposure coefficients that remained in a relatively narrow range (from 0.0002 to 0.0008).[15] The HEI (1999) concluded that the Steenland-study "*may provide reasonable estimates of worker exposure to diesel exhaust, but significant further evaluation and development are needed*" to improve the use in quantitative risk assessment.[27] By changing assumptions on specifically emissions and dieselisation, Bailey et al. (2003) found lower mean exposure levels for short-haul drivers in all years compared to the levels predicted by Steenland et al.[29] They also suggested that it was not necessary to adjust for possible exposure to DEE in the driver's compartment of older, poorly-maintained trucks, as Steenland et al. did, because most companies

which participated in the study used newer trucks. According to the DECOS, the suggestions made by Bailey et al. would indicate an overestimation of the actual historical exposure levels in the Steenland study, and thus of an underestimation of the lung cancer risk. Regarding Garschick et al. (2012) and Silverman et al. (2012), the HEI (2015) concluded that the uncertainties in exposure are sufficiently discussed and analysed, and that the estimated historical exposures are reasonably accurate (a summary of the findings by HEI is given in Annex A).[26] In addition, Crump et al.(2015) extended the analyses of the study by Silverman et al. by using six alternative models for estimating the historical measures of REC exposure.[35] These additional sensitivity analyses demonstrated the robustness in the association between lung cancer mortality and alternative estimates of REC exposure. In the study by Möhner et al. (2013) it was assumed that the working conditions of local engineers and industrial hygienists had been constant over the past years.[16] Therefore, the workers' historical exposure was based on one time point. Whether exposures had indeed been constant over the years, was not verified. In addition, it is not clear to the DECOS to what degree the exposure matrix reflects the historical working situation, since no details were given on the conversion factor that was used to derive the exposure matrix.

Based on the sensitivity analyses performed by the authors or by others, the DECOS agrees with the HEI (2015) that the historical exposure estimates in the studies by Silverman et al. (2012) and Garshick et al. (2012) were reasonably accurate. This finding does not preclude the two studies for quantitative risk assessment. The historical exposure estimates in the study by Steenland et al. (1998) are most likely less accurate. On the other hand, for the Steenland study several exposure scenarios are available, so that the DECOS does not exclude the study for quantitative risk assessment. Regarding the study by Möhner et al. (2013), the DECOS is of the opinion that more information is needed on the methods used to estimate historical exposures, to get an idea on the accuracy of the estimates, and on the usefulness in quantitative risk assessment.

Smoking status

Smoking is strongly associated with lung cancer, and thus may have influenced DEE-induced lung cancer risk estimates. Some data were presented on smoking status. Silverman et al. (2012) collected data on individual smoking status by holding interviews with the workers themselves or their next of kin. The authors performed sensitivity analyses, and found that smoking significantly increased the odds of DEE-induced lung cancer, although the outcomes were variable depending on smoking status, intensity and work location (Silverman et al. 2012, Silverman et al. 2014).[17,39] In the Garshick study, data on smoking habits were retrospectively collected (based on job titles); no data on individual smoking status were available. Since both job titles and smoking habits are related to the socioeconomic status, the authors performed a sensitivity analysis on smoking status, and concluded that

adjustment only modestly reduced the cancer risk among long-haul drivers. Also, they noticed that the smoking rates in their cohort were similar to the rates in the general population. Based on these findings, the authors concluded that it was unlikely that smoking would have an appreciable influence on the DEE exposure-response relationship. The HEI (2015) also evaluated the controlling for smoking in the studies by Silverman et al. and Garshick et al., and used alternative metrics to evaluate the impact of adjusting for smoking habits.[26] The HEI concluded that the methods for adjusting for smoking were sufficiently appropriate, although individual data are preferred to prevent misclassification. An issue related to smoking habits is the suggestion made by others that the risk of lung cancer from smoking would differ for underground miners compared to surface only workers, and that this difference could have influenced the outcome of the risk analyses.[16,20,40] However, whether different working populations have different risk ratios for lung cancer, is according to the HEI panel a matter of debate. Steenland et al. (1998) obtained information on smoking histories from interviews of the next of kin, and adjusted their data for smoking status and intensity.[15] No data were presented which were not adjusted for smoking, but the authors stated that current or past smoking increased the odds ratio for lung cancer when data on never smokers were used as reference value. Möhner et al. (2013) collected data on smoking habits from company medical records.[16] They showed that ‘ever’ smokers had a higher lung cancer mortality risk than ‘never’ smokers. The DECOS noted that this analysis was based on a very low number of cases, partly because data on smoking status were available for only 47.1% and 54.7% of the participants. The low number of cases introduces a degree of uncertainty on the influence of smoking on DEE-induced lung cancer risk, so that according to the DECOS no firm conclusion can be made.

The DECOS noted that in the studies data on smoking status were mainly obtained from secondary sources, introducing some degree of information error. The DECOS adds that if the population under study is comparable with the reference group, it is most likely that the lifestyles are roughly comparable, and probably also the smoking habits between the two populations. As smoking is considered by the DECOS as an independent risk factor, this would mean that the relative differences in mortality between the exposed groups and the reference group are unlikely to be due to smoking. Therefore, the DECOS does not preclude the studies for quantitative risk assessment.

‘Healthy worker’ effect

Observational studies, in particular those with a case-control or retrospective design may be prone to the ‘healthy worker’ effect. This effect underestimates the actual risk, because the observed working population appears to be healthier than expected. This is explained by the fact that any worker with complaints or diseases has left the workplace before the investigation began. However, in the literature it is suggested that the healthy worker effect occurs mainly with diseases which develop

in the short term. An issue regarding the healthy-worker effect is that Garshick et al. (2012) used an adjustment method for 'healthy worker survivor bias' by including duration of employment.[18] Without this adjustment, there was no strong evidence of a trend in the exposure-response. The DECOS noted that the method of adjustment for the healthy worker effect is not used commonly, as cumulative exposure contains already a measure of duration, which can lead to overestimated cancer risks. The HEI (2015) considered that duration of employment on its own brings along some uncertainty: the longer the duration of employment the higher the possibility of workers dying from diseases other than cancer.[26] Therefore, the HEI (2015) concluded that the adjustment made by Garshick et al. does not preclude the study from being used in quantitative risk assessment.

Overall, the 'healthy worker' effect may have resulted in an underestimation of the lung cancer risk in all studies to some degree. According to the DECOS, however, it is reasonable to assume that this phenomenon has only a minor influence on the level of lung cancer mortality risk. Therefore exclusion of the studies for quantitative risk assessment is not necessary.

Former employment

Former employment in other high-risk occupations for lung cancer could bias the DEE-induced lung cancer risk estimates. As the average age of starting work in the trucking industry was 25 years, Garshick et al. (2012) stated that some workers had a work history of up to 10 years in the trucking, or other high-risk industries, which would reduce their risk estimates.[18] More specifically, Silverman et al. (2012) explored whether former employment influenced the cancer risk estimated in the non-metal mining industry.[17] They found an association between lung cancer risk and over ten years of former employment in other industries with high-risk occupations (odds ratio 1.14 [95% confidence interval 1.06-2.91], 39 cases/68 controls) compared to miners without former employment. However, they did not include this potential confounding in their risk calculations, because it only had a minor influence on the outcome (less than a 10% change in odds ratio). In addition, Möhner et al. (2013) showed in a sub-analysis on previous employment in uranium mining (ever/never; 7 cases; odds ratio 3.65, [95% confidence interval 1.20] -11.14, conditional logistic regression) that lung cancer risk was statistically significantly increased compared to a reference group (no employment in mining or heavy industries).[16] They suggested that the significant increase in lung cancer risk in former uranium miners was caused by an overall increased disease risk as a result of co-exposure (e.g., high exposure to radon and respirable quartz dust). No associations were found between other former jobs (other mining or heavy industries) and lung cancer risk. Steenland et al. (1990, 1998) did not discuss former employment as a possible confounding factor.[15,28]

Overall, there are indications that former employment in a high-risk occupation may have influenced the risk estimates to some extent. To

what degree is uncertain to the DECOS, however, it is reasonable to believe that it did not have a major influence, especially when considering data on long duration of employment.

Co-exposure in the mining industry

Another confounding risk factor that may have influenced the outcomes is co-exposure to potential carcinogenic substances from sources other than from DEE-sources in the mining industry, such as dust, silica, asbestos and radon. For this reason, Silverman et al. (2012) selected non-metal mines to prevent high exposure to these potential risk factors.[17] In addition, Attfield et al. (2012) and Silverman et al. (2012) showed data on exposure levels of various substances to which miners may be exposed in the Silverman-study.[17,33] Exposure-response data were presented for the individual substances, and the effect of each of these substances on the risk analysis of DEE exposure was investigated. The sensitivity analyses revealed a small increase (overall 5%, all below 10%) in the hazard risk estimated for REC. Because of the small effect, Silverman et al. did not include these risk factors in their final models used for the risk analyses. Still, in the literature, it is suggested that radon exposure influenced the outcome of the Silverman study.[16,20,22] Radon is a well-known human carcinogen. Crump et al. (2015) showed in their sensitivity analysis that additional adjustment for radon resulted in a much weaker effect of REC on lung cancer mortality, and when adjusted, did not find an association between DEE-exposure and lung cancer mortality.[35,36] The HEI (2015) discussed the validity that radon may have contributed to at least a portion of the lung cancer burden among underground miners in the Silverman-study.[26] It concluded that "*radon exposure was not critically important and could itself lead to unintended bias*", and that the radon levels in the underground mines were well below the current standards set by the American National Institute for Occupational Safety and Health, the Mine Safety and Health Administration standard, and the Occupational Safety and Health Association. Furthermore, the HEI noted that the levels of airborne radon in underground mines are relatively constant, which suggests 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. Therefore, according to the HEI it is almost impossible to disentangle the cumulative exposure to EC and radon in a sensitivity analysis; instead it weakens the validity of the analysis.

Regarding co-exposure to radon, and in line with the HEI, the DECOS is of the opinion that it is unlikely that radon exposure may have influenced the outcomes in the Silverman study, and that adjustment for radon is not necessary. The reason being the very low levels of radon in the Silverman study, which were well below the existing occupational exposure levels for radon. In addition, Cao et al. (2017) predicted that 9 to 26 percent of the lung cancer deaths caused by radon exposure actually account for diesel exposure.[37] If that is the case, this would suggest that corrections for

radon exposure could lead to an underestimation of the actual lung cancer risk caused by DEE exposure in miners.

Work location in the mining industry

Attfield et al. (2012) and Silverman et al. (2012) observed different patterns of lung cancer mortality between workers in underground mines and 'surface only' workers; the underground miners being exposed to higher average levels of REC, but showing lower lung cancer mortality, and having a different smoking status pattern, than 'surface only' workers.[17,33] On the other hand, cumulative exposure between the two groups was comparable, suggesting that underground miners were exposed for a shorter time period. A further subgroup analysis performed by Crump et al. (2015) and Moolgavkar et al. (2015), showed that 'ever' underground miners had a higher lung cancer mortality risk than 'only' underground miners.[35,38] However, the further subgroup division also lowered the precision of the estimates. Therefore, the HEI (2015) concluded that it was better to rely on the estimates without subgroup division.[26] The DECOS agrees with the conclusion by the HEI (2015).

Conclusion

The DECOS is of the opinion that the studies by Garshick et al. (2012, trucking industry) and Silverman et al. (2012, non-metal mining industry) have adequately addressed the issues of bias and confounding, and concludes that their risk analyses are of sufficient quality to be used for deriving HBC-OCRVs. This is in line with the conclusion by the HEI (2015), that "*both studies were well-designed and well-conducted, and could provide a good starting point for a quantitative risk assessment*".[26] Also, Steenland et al. (1998; trucking industry) addressed the uncertainties in historical exposure levels and smoking habits. Although the exposure predictions are probably overestimated to a certain degree, the DECOS concludes that data from this study can be used in deriving HBC-OCRVs. The DECOS considers the study by Möhner et al. (2013) less suitable for quantitative risk assessment, because of: the high mean cumulative exposure level (1st tertile < 983 µg REC/m^3-years; mean 624 µg REC/m^3-years) in the reference group compared to almost all reference cumulative exposure levels in the other three studies; insufficient explanation on how exactly the authors adjusted the risk analysis on cumulative exposure for smoking combined with former employment; and the relative high percentage of missing data on smoking status and former employment.

6.3 Point of departure in deriving HBC-OCRVs

The DECOS has a few options in deciding which study can best be used in deriving HBC-OCRVs: the study with data on the lowest exposure levels, the study resulting in the lowest calculated HBC-OCRVs, or a meta-analysis. A meta-analysis is a statistical analysis that combines the results of a number of conceptually similar scientific studies to derive pooled risk estimates. A benefit of a meta-analysis is that it increases the

statistical power, and that it gives a more precise and robust risk estimate than the individual studies. Possible drawbacks of a meta-analysis are the high degree of heterogeneity among the studies, the fact that data are not comparable and cannot be combined, shortcomings in the statistical effect models used, and incorrect criteria for the inclusion and exclusion of the individual studies. Because of the benefits provided by a meta-analysis, the DECOS examined whether a meta-analysis could serve as base to derive HBC-OCRVs.

In the literature, three meta- or pooled analyses have been published, which were based on Steenland et al. (1998), Garshick et al. (2012), Silverman et al. (2012), and/or Möhner et al. (2013). MacCalman et al. (2015) included the data by Garshick et al., and Silverman et al., reducing the estimated exposure levels in the latter study by 25%.[19] Morfeld and Spallek (2015) made several exposure adjustments to the data collected by Steenland et al., Garshick et al. or Silverman et al.[24] They also performed supplementary analyses which included data from Möhner et al. using new exposure categories. Vermeulen et al. (2014) used data from Steenland et al., Garshick et al. and Silverman et al. without supplementary exposure adjustments, and in a sensitivity analysis, they included data from the study by Möhner et al.[10]

Overall, comparison of the outcomes of the three analyses showed that adjusting exposure, including or excluding certain sets of data, using different regression models, or using different lag-times, may change the risk estimates to some extent, but according to the DECOS, not substantially. Therefore, the DECOS decided to use the meta-analysis that included the three individual studies, which in the opinion by the DECOS, should be considered, and which stayed closest to the original data and did not involve making exposure adjustments afterwards. This means that the DECOS prefers using the meta-analysis by Vermeulen et al. in deriving HBC-OCRVs. A description of the meta-analysis is given below, while further details are presented in Annex B.

Vermeulen et al. (2014) performed a detailed literature search and included studies which had exposure data expressed as cumulative EC in the exposure-response analyses, an appropriate unexposed/low exposed reference group and no major methodological shortcomings.[10] Only three studies met the criteria: Steenland et al. 1998, Garshick et al. 2012, and Silverman et al. 2012. These studies have all been described extensively in the preceding section. The study by Möhner et al. (2013) was excluded because of the high cumulative exposure of the reference group, the lack of detail on the derivation of the EC exposure metric, and questions about the methods used to adjust for previous employment.

The authors used as relative risks (RR) the odds ratios for cumulative EC exposure categories with a 5 year lag from Steenland et al. (1998), the hazard ratios for cumulative EC exposure categories with a 5 year lag (excluding the mechanics) in the Garshick study, and the odds ratios for cumulative EC exposure with a 15 year lag from Silverman et al. (2012).

For each exposure category, study-specific categorical RRs were estimated for lung cancer mortality. The midpoint of each exposure category was used as a specific estimate of cumulative exposure for each RR. The midpoint of the highest exposure category was estimated to be 5/3 times the lower bound of the category, except for the highest category in the Silverman-study, in which the median value was chosen. From the three studies, 10 study-specific categorical RR estimates for lung cancer mortality were extracted, covering a cumulative exposure range from 37 to 1,036 µg REC/m^3-years.

A full linear meta-regression model was used, and a model that incorporated a natural spline function. To account for any potential heterogeneity between the studies, the regression models allowed for random study-specific intercepts and exposure effects. In addition, a series of sensitivity analyses were performed to examine the impact of lag time (no lag, 10 year lag), and inclusion of the mechanics in the study by Garshick study, on the (pooled) exposure-response model. Also, sensitivity analyses were performed by including original and adjusted risk data from Möhner et al. (2013). In a separate publication, additional sensitivity analyses were performed, leaving out, for instance, data from Steenland et al., Garshick et al., or Silverman et al.[43]

Figure 1 shows the predicted exposure-response curve, based on a log-linear model. The dark grey shaded area represents the 95% confidence interval estimates. Combining the three studies, a pooled slope (β) factor of the exposure-response curve was estimated of 0.00098 (logarithm of the RR (lnRR) for a 1 µg/m^3-year increase in REC; 95% confidence interval, 0.00055 – 0.00141). For the individual studies it ranged between 0.00061 and 0.0012 with 95% confidence intervals largely overlapping each other. Background exposure was taken into account for the lowest exposure groups, i.e., the intercept approached the background levels.

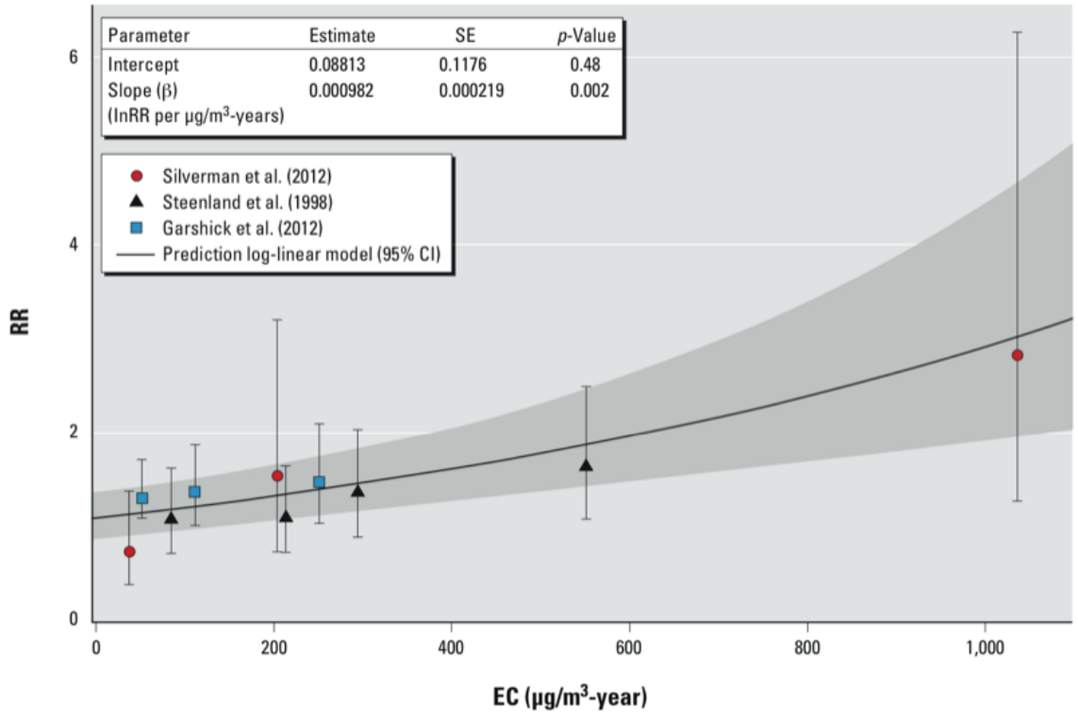

Figure 1. Predicted 'pooled' exposure–response curve of cumulative EC and relative risk of lung cancer mortality, Vermeulen et al. (2014).[10] SE, standard error; 95% CI, 95% confidence interval

The slope factors of the sensitivity analyses ranged between 0.00061 and 0.0012, which is not substantially different from the main estimate of 0.00098 (within a factor of two). Based on the results of the sensitivity analyses, Vermeulen et al. concluded that the pooled slope factor estimate appears to be relatively robust.

Uncertainties and limitations

Vermeulen et al. reported that they were not able to perform formal tests on heterogeneity, because of the small number of data points for each study. For the same reason they were not able to examine other regression models. Also, they noted that the exposure lag time differed among the studies (5 years and 15 years). However sensitivity analyses using different lag times (no lag, 10 year lag) were generally consistent with the main analysis.

The data used in the meta-analysis are based on studies of populations of the United States of America (USA). This raises the question as to whether the European population is comparable with that of the USA. Epidemiological studies on lung cancer and job title/years worked conducted in the European population show effects comparable to studies in the US population (see the NEG-DECOS criteria documentation, Tables 19 and 20).[1] Therefore, the DECOS considers the results of the meta-regression valid for the European population, including the Dutch population.

6.4 Calculation of the HBC-OCRVs

Based on the predicted exposure-response curve calculated in the meta-analysis by Vermeulen et al. (see Figure 1), the DECOS estimated the HBC-OCRVs. A HBC-OCRV 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 caused by 40 years of occupational exposure, which are added to the number of cases of lung cancer death per 1,000 (4×10^{-3}) and 100,000 (4×10^{-5}) cases of death (all causes) in the general population. As an example, in the Netherlands, of every 100,000 men who died in 2017, about 8,400 died of lung cancer (8.4%; source Statistics Netherlands). Forty years of occupational exposure should not lead to more than 8,404 (4 plus 8,400) cases of lung cancer death per 100,000 general deaths cases, or 88 (4 plus 84) cases of lung cancer death per 1,000 general death cases in the population. Essentially, the DECOS translates these absolute risks to relative risks, so that the corresponding exposure concentration can be read out on the exposure-response curve. In epidemiology, the risk of exposure-related cancer is generally expressed as a relative risk.

In addition, the DECOS prefers using life-table analyses to calculate extra risk of cancer. By using life tables, death resulting from causes can be accounted for. Furthermore, life-table analysis makes accounting for time

and age-dependent factors in the development of cancer, such as latency, possible. In the Guideline for the Calculation of Occupational Cancer Risk Values, the DECOS provides detailed information on the use of this analysis.[44] 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 years and gradually builds up till the age of 60 years. The cohorts gradually reduce in size because of lung cancer mortality and mortality resulting from other causes of death. Excess risk calculations were truncated at the age of 100 years, 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). The concentrations of REC, 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 of REC (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 DECOS estimated that the HBC-OCRVs of REC in DEE powered by petroleum-diesel fuels, which corresponds to

- 4 extra death cases of lung cancer per 100,000 (4×10^{-5}), for 40 years of occupational exposure, equals to 0.011 μg REC/m^3,
- 4 extra death cases of lung cancer per 1,000 (4×10^{-3}), for 40 years of occupational exposure, equals to 1.03 μg REC/m^3.

The HBC-OCRVs are expressed as 8-hour time-weighted average concentrations (8 hour TWA).

Remarks on the calculated HBC-OCRVs

Preference of exposure parameter

The recommendation made by the DECOS is based on using REC as the exposure parameter. The carcinogenic components in DEE are mainly found in the particulate matter of DEE. Elemental carbon: a) constituted a large portion of the particulate matter of DEE from diesel engines before the introduction of the new technologies to reduce emission of hazardous compounds (30-90% of the particulate mass); b) is a more specific and sensitive marker of exposure to diesel engine particulates compared to

measuring gravimetrically respirable particle size fractions; and c) mechanically generated particles from sources other than DEE, can be efficiently separated by size-selective sampling techniques. These reasons justify the use of EC as the exposure parameter. The DECOS emphasises that there are no suggestions that EC is a lung carcinogen, but rather that it represents a marker of exposure to carcinogenic components in the particulate matter of DEE.

Value of HBC-OCRVs for petroleum-diesel powered engines emitting DEE without particles

The HBC-OCRVs are based on data from studies in which workers were exposed to exhaust from diesel engines in use before the latest technologies for reducing emission of diesel exhaust particles. This raises questions about the utility of the recommendation when workers are exposed to DEE emitted by diesel engines which have been modified by the newest technologies and contain filter systems to capture particulate matter. Although the proportion of EC in particulate matter that is emitted by new technology engines has been reduced, EC can still be present depending on the type of engine, the diesel fuel and the use of after-treatment systems (average 13 % of the particulate mass in heavy-duty engines). However, EC may not be an equally useful marker for exhaust emitted from new technology diesel engines with significantly reduced particle mass and EC concentration,. Alternative exposure markers (e.g., nitrogen dioxide or nitrogen oxides) in the prevention of cancer are not useful, because of a lack of epidemiological data on specificity, sensitivity and exposure-response relationships (for an overview of health effects and exposure-response relationships of DEE from new and old technology diesel engines see Table 22 in the NEG-DECOS criterion documentation). Furthermore, whether the lowered emission of diesel engine particles achieved by applying new technologies, also poses a lower cancer risk is unclear. Limited data from one long-term animal experiment point towards this direction (see NEG-DECOS criteria documentation). However, observational studies on long-term exposure are not (yet) available. In addition, other issues have been given little attention up to now, such as the potential role of nanosized particles on the carcinogenicity, which contribute very little to the diesel engine particle mass.

Protection of the HBC-OCRVs against non-carcinogenic adverse health effects

An HBC-OCRV should prevent or limit any adverse health effects, including non-cancer adverse health effects. In the case of DEE no noticeable adverse health effects should occur below the recommended exposure concentration of 1.03 µg REC/m^3, which corresponds to an excess cancer risk of 4 deaths per 1,000.

Exposure to DEE is also associated with, for instance, inflammatory lung and cardiovascular effects. Few exposure-response data have been published on human and animal experiments (see Chapter 10 and 11 in the NEG-DECOS criterion documentation). Table 22 in the NEG-DECOS

criterion documentation gives an overview on the lowest observed adverse effect levels found in human and animal inhalation experiments. As the volunteers in human experiments were only exposed once for a very short time (1-2 hours), and these studies were not assessed to examine exposure-response relationships, it cannot be excluded that below 100 µg DEP/m^3 (~75 µg REC/m^3; 0.38-0.76 mg NO_2/m^3; the lowest exposure levels tested showing effects), pulmonary or cardiovascular adverse health effects occur as a result of single or chronic exposure. No reliable exposure-response data from observational studies are available. The number of animal experiments on non-cancer adverse health effects in the exposure range of the HBC-OCRVs is limited. In an animal experiment, in which rats were exposed sub-chronically (13 weeks) or chronically (130 weeks) to DEE emitted from a new technology engine, the lowest exposure levels at which histopathological changes in rat lungs have been observed, were around 10-12 µg DEP/m^3 (~7.5-9 µg REC/m^3; 6.9-8 mg NO_2/m^3); in the same animal study no pulmonary effects were observed below 5 µg DEP/m^3 (~3.8 µg REC /m^3; 1.7 mg NO_2/m^3). No cardiovascular pathology was found in rats that were chronically exposed to diesel exhaust extracts by inhalation for two years at a concentration as low as 3 µg DEP/m^3 (~ 2,3 µg REC/m^3). More animal data are available at much higher exposure levels. Several chronic animal studies (rats) have demonstrated inflammatory lung effects and lung fibrosis at exposure levels exceeding 800 µg DEP/m^3 (~600 µg REC/m^3).

Data from studies investigating the relationship between traffic-related air pollution and causes of mortality in the general population, revealed that exposure per 1 µg EC/m^3 increases all-cause mortality by 6% ([95% confidence interval 5-7%]; pooled estimate). For exposure per 10 µg NO_2/m^3 it was estimated to increase all-cause mortality by 5.5% ([95% confidence interval 3-8%]; pooled estimates).[45] The DECOS notices differences between the traffic-related and the work-related studies. Exposure to traffic-related air pollution is studied in the general population, throughout life and include vulnerable people, whereas occupational exposure is studied in healthy people during the work period only. Furthermore, the composition of traffic-related air pollution differs to some extent from the composition of DEE, because of a larger diversity in types of engines and fuels. For these reasons the results from the traffic-related studies are not directly comparable with the results of the work-related studies.

Overall, the DECOS noted that the number of studies in which exposure levels were used in the range of the derived HBC-OCRVs is limited. However, the available data from experiments with healthy humans and animals indicate that inflammatory lung effects and adverse cardiovascular effects are generally induced at higher exposure levels than the HBC-OCRV of 1.03 µg REC/m^3. Therefore, the DECOS considers it likely that the HBC-OCRV will sufficiently protect against inflammatory lung and adverse cardiovascular effects.

6.5 Conclusion and recommendation

The DECOS estimates that the HBC-OCRVs of REC in DEE powered by petroleum-diesel fuels, which corresponds to:

- 4 extra death cases of lung cancer per 100,000 (4×10^{-5}), for 40 years of occupational exposure, equals to 0.011 µg REC/m^3,
- 4 extra death cases of lung cancer per 1,000 (4×10^{-3}), for 40 years of occupational exposure, equals to 1.03 µg REC/m^3.

The HBC-OCRVs are expressed as 8-hour time-weighted average concentrations (8 hour TWA).

6.6 Short-term exposure limit (STEL)

A STEL (15 minute time-weighted average concentration) is assessed when a relevant adverse health effect is expected to occur after short-term exposure, and the association between exposure concentration and health effect follows a steep exposure-response relationship. A STEL is, furthermore, applied when the control for adverse health effects is not sufficiently covered by a HBR-OEL or HBC-OCRV (8 hour TWA). In healthy humans, single exposure to 100-300 µg DEP/m^3 (≈ 75-225 µg EC/m^3; ≈ 2.5 mg NO_2/m^3) of elemental carbon or diesel engine particulate may induce pulmonary inflammation and a slightly increased airway resistance (see Chapters 9 and 10 in NEG-DECOS criterion documentation). These acute effects may be caused by a combination of exposure to DEP and nitrogen oxides. However, the DECOS does not consider it necessary to derive a STEL, because the clearance of diesel engine particles in the lungs has a long half-life time of several months.[12,13,46] The DECOS is aware that for NO_2 alone, in the Netherlands, a legally binding STEL is set at 1 mg NO_2/m^3. However, deriving a STEL for DEE on NO_2 alone is insufficient to cover the complex mixture of DEE.

6.7 Classification of DEE as toxic to reproduction

Because of a lack of data no recommendation on the possible reproduction toxic properties of DEE is given.

6.8 Skin notation

A skin notation for a substance is recommended when data indicate a substantial contribution of dermal exposure to systemic adverse health effects, on which a health-based OEL or HBC-OCRVs are based. In the case of DEE, the composition of DEE means that no substantial dermal absorption is expected. Therefore, the DECOS does not recommend a skin notation.

6.9 Groups at extra 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. People with a greater risk of lung cancer, such as smokers, may be more vulnerable to develop lung cancer from DEE exposure.

07
research needs

Numerous studies have been published on the adverse health effects 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 NO_x. Also, it is unknown what 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, in particular in automobile transportation. Despite this trend, the committee expects that it will take many years before electric engines replace all diesel engines, in particular 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 overview key studies

	Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
Study design and population				
Design	Nested case-control	Retrospective cohort (Trucking Industry Particle Study/Truckers study)	Nested case-control (DEMS-study)	Nested case-control
Country	USA	USA	USA	Germany
Study period/ period of data collection	1949 (year that diesel fuel began to be used in appreciable quantities) – 1990; exposure analyses based on data of 1983	1985-2006	1947 (introduction diesel equipment) - 1997	1970 (introduction of diesel-powered vehicles) - 2001
Type of industry	Trucking industry	Trucking industry	Mining industry (non-metal)	Potash mining industry
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	Maintenance/workshop workers, production workers
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 per facility (N_{total}=12,315). These mines were chosen because of known low exposure to potential lung cancer substances other than DEE (including radon, silica, asbestos and PAHs)	6 potash mines in the South Harz region of Eastern Germany (N=5,819 male workers)
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	Cases (N=68): lung cancer deaths Controls (N=340): 5 controls were matched with each lung cancer case, based on 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)	Employed for at least 1 year after 1969

	Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
Average age at start of study/ data collection	n/a	1985: 49.1 ± 6.0 yrs	n/a	Year of birth, 1929 (range 1913-1946); age at hire (years), 27,6 (range 14.0-49.5); age at exposure start (years), 41.3 (range 25.4-56.6)
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		Subgroups, jobs before potash mining: - no employment in mining or heavy industries (N=16 cases) - employment in uranium mining (N=7 cases) - employment in other mining or heavy industries (N=6 cases) - no employment in uranium mining, but missing information on other employment outside potash mining (N=39 cases)
Original study	Case-control study (Steenland et al. 1990)[28]	Retrospective cohort study (Laden et al. 2007, Garshick et al. 2008)[30,31]	Retrospective cohort study (Coble et al. 2010; Stewart et al. 2010, 2012; Vermeulen et al. 2010a, 2010b, Attfield et al. 2012)[33,34,47-50]	Retrospective cohort study (Säverin et al. 1999, Neumeyer-Gromen et al. 2009)[41,51]
Exposure assessment				
Marker DEE exposure	Sub-micrometer EC (EC_{sub}), cumulative	EC, cumulative and average	REC (REC), cumulative and average	REC (REC), cumulative
Exposure assessment	Historical levels of exposure linked to known work history	Historical exposure linked to work records to estimate personal exposure	Historical exposure linked to type of jobs, work location	Historical exposure linked to total carbon measurements in 1991; job-exposure-matrix;
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	Based on total carbon measurements from 1991, estimates made for type of job (production, maintenance and workshop); REC levels based on correction factor (proportion of weight of EC in total carbon, 63%); job history based on medical records Total duration of exposure was at maximum 22 year, because the mines were closed in 1991

	Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
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	1991 (airborne total carbon measurements)
Personal exposure estimation	Assumption (1): average 1990 levels for job category could be assigned to all subjects in that category Assumption (2): levels before 1990 were proportional to vehicle moles travelled by heavy duty trucks and the estimated emission levels Assumption (3): long-haul drivers received some exposure from their own truck Time-dependent cumulative exposure modelled in lags of 0 and 5 years	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 15-year lag	Time-dependent exposure modelled in lag of 5 years
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	Assumption (1): since mining equipment remained fairly stable since 1969, exposure data from 1991 are used for designing a job-exposure-matrix
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	Mean (all cases): 1,436 µg/m^3-years (range 302-3,226 µg/m^3-years)
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	Companies medical records, local population registers, cemeteries and parish offices, and Federal-State (health) archive
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)	Lung cancer (ICD-9, code 162; ICD-10, code C34)

	Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
Effect endpoint	Lung cancer death	Lung cancer death: 779 cases (734 underlying cause) Total number of deaths: 4,306	Lung cancer death	Lung cancer death
Exposure-response relationship				
Method	Logistic regression	Proportional hazard regression	Conditional logistic regression	Conditional logistic regression, assuming a linear dose-response relationship, based on percentiles of cumulative exposure
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)	Smoking habits, jobs held before potash mining
Sensitivity analysis	Total duration of employment	Total duration of employment	No data	No data
Association with average exposure	No data	HR, hazard ratio $^{U/A}$ unadjusted/adjusted for duration of work 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):*	OR, Odds ratio CI, 95% confidence interval N = cases/controls **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	No data

Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
	HR^{U} = 1.15 (CI 0.93-1.43) HR^{A} = 1.15 (CI 0.93-1.43) *5.4-7.9 µg/m^3 (N=221):* HR^{U} = 1.11 (CI 0.89-1.39) HR^{A} = 1.12 (CI 0.89-1.40) *≥ 7.9 µg/m^3 (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	**15-year lag, all workers** *0-1 µg/m^3 (N=47/190)*: OR = 1.00 (reference) *1-32 µg/m^3 (N=52/187)*: OR = 1.11 (CI 0.59-2.07) *32-98 µg/m^3 (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/m^3 (N=29/81):* OR = 1.00 (reference) *8-49 µg/m^3 (N=29/73):* OR = 1.04 (CI 0.45-2.43) *49-104 µg/m^3 (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 **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*:	HR, hazard ratio $^{U/A}$ unadjusted/adjusted for duration of work CI, 95% confidence interval N = number of cases **No lag, all workers** *< 530 µg/m^3-months (*N=153): HR^{U} = 1.00 (reference) HR^{A} = 1.00 (reference) *530-1,061 µg/m^3-months (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-months (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-months (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	R, Odds ratio CI, 95% confidence interval **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, Odds ratio CI, 95% confidence interval Not adjusted/adjusted for smoking habits and occupational history Standard mortality ratios (SMR) CI, 95% confidence interval N=observed/expected cases **5-year lag, all workers** 0-982 *µg/m^3-yr:* OR = 1.00 (reference) 983-1,550 *µg/m^3-yr:* OR = 1.48 (0.74-2.94)/1.77 (0.85-3.69) > 1,550 *µg/m^3-yr:* OR = 0.86 (0.40-1.82)/1.04 (0.47-2.27)

Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
OR = 1.36 (CI 0.90-2.04) *> 331 µg/m³-years*: OR = 1.64 (CI 1.09-2.49) *p* for trend = 0.032	**No lag, without mechanics** *< 530 µg/m³-months (*N=153): HR^{U} = 1.00 (reference) HR^{A} = 1.00 (reference) *530-1,061 µg/m³-months (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/m³-months (N=202):* HR^{U} = 1.13 (CI 0.87-1.46) HR^{A} = 1.30 (CI 0.99-1.72) *≥ 2,076 µg/m³-months (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/m³-months (*N=122): HR^{U} = 1.00 (reference) HR^{A} = 1.00 (reference) *371-860 µg/m³-months (N=193):* HR^{U} = 1.18 (CI 0.92-1.51) HR^{A} = 1.30 (CI 1.01-1.68) *860-1,803 µg/m³-months (N=208):* HR^{U} = 1.16 (CI 0.88-1.53) HR^{A} = 1.35 (CI 1.01-1.81) *≥ 1,803 µg/m³-months (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-months (*N=122): HR^{U} = 1.00 (reference) HR^{A} = 1.00 (reference) *371-860 µg/m³-months (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-months (N=202):*	OR = 1.81 (CI 0.8-3.89) *≥ 1465 µg/m³-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/m³-y (N=49/158)*: OR = 1.00 (reference) *3-72 µg/m³-y (N=50/228)*: OR = 0.74 (CI 0.40-1.38) *72-536 µg/m³-y (N=49/157)*: OR = 1.54 (CI 0.74-3.20) *≥ 536 µg/m³-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/m³-y (N=29/92)*: OR = 1.00 (reference) *81-325 µg/m³-y (N=29/52)*: OR = 1.18 (CI 0.52-2.68) *325-878 µg/m³-y (N=29/69)*: OR = 0.84 (CI 0.39-1.82) *≥ 878 µg/m³-y (N=29/51)*: OR = 2.08 (CI 1.01-4.27) *p* for trend = 0.062	**5-year lag, all but former uranium miners** *0-1,076 µg/m³-yr (N=20/28.11):* SMR = 0.71 (0.43-1.10) *1,076-1,691 (N=17/18.11):* SMR = 0.94 (0.55-1.50) *≥ 1,691 µg/m³-yr (N=18/18.78):* SMR = 0.96 (0.57-1.51) **5-year lag, only miners without previous employment in mining or heavy industries** *< 1,512 µg/m³-yr (mean, 617 µg/m³-yr) (N=7/14.22):* SMR = 0.49 (0.20-1.01) *≥ 1,512 µg/m³-yr (mean, 2,274 µg/m³-yr) (N=6/11.32):* SMR = 0.53 (0.19-1.15)

Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
	HR^{U} = 1.17 (CI 0.88-1.55) HR^{A} = 1.38 (CI 1.02-1.87) *≥ 1,803 µg/m^3-months (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/m^3-months (*N=114): HR^{U} = 1.00 (reference) HR^{A} = 1.00 (reference) *167-596 µg/m^3-months (N=183):* HR^{U} = 1.04 (CI 0.79-1.37) HR^{A} = 1.14 (CI 0.86-1.52) *596-1,436 µg/m^3-months (N=205):* HR^{U} = 1.01 (CI 0.74-1.37) HR^{A} = 1.18 (CI 0.85-1.64) *≥ 1,436 µg/m^3-months (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/m^3-months (*N=112): HR^{U} = 1.00 (reference) HR^{A} = 1.00 (reference) *167-596 µg/m^3-months (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-months (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-months (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		

	Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
		Note: cumulative exposure expressed in µg/m^3-years is cumulative exposure in µg/m^3-months divided by 12		
Study design and population				
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	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	No data

	Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
	Short-haul driver 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	No association found after adjusting for smoking habits and employment before potash mining
Notes as indicated by the authors				
General	Results depend on broad assumptions and are limited by a variety of factors			

	Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
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 workers this could contribute to negative confounding when the results are not adjusted for duration of employment; to keep a commercial driver license, drivers need to undergo medical examinations, which may select more healthier drivers that continue to work	(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 and DEE exposure on lung cancer risk (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 µg EC/m^3-yrs: OR = 1.47 > 304 µg 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 µg EC/m^3-yrs: OR = 1.12 > 304 µg EC/m^3-yrs: OR = 2.40 (6) proportion smokers in study was substantially lower than in general population (29% versus 51%)	Standard mortality ratios (SMR) CI, 95% confidence interval N=observed/expected cases Smoking status: *Never smoker (N=2/20.53):* SMR = 0.10 (0.01-0.35) *Ever smoker (N=31/26.84):* SMR = 1.29 (0.85-1.86) *Status unknown (N=31/26.84):* SMR = 1.16 (0.78-1.64)
Former employment	No data	No data	No data	Standard mortality ratios (SMR) CI, 95% confidence interval N=observed/expected cases Employment before potash mining: *No such an employment (N=13/25.53)*: SMR = 0.51 (0.27-0.87) *Uranium mining (N=6/4.13):* *SMR* = 1.45 (0.53-3.16) *Other mining/heavy industry (N=5/6.17)*: SMR = 0.81 (0.26-1.89) *Not stated, but no uranium mining (N=37/33.29)*: SMR = 1.11 (0.48-1.53) *Total (N=61/69.13)*: SMR = 0.88 (0.67-1.13)

	Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
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**	**Möhner et al. 2013**
HEI report (2015)[26]	Not reviewed	*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	*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;	Not reviewed

Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
	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 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	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 *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	Not reviewed

	Steenland et al. 1998[15]	Garshick et al. 2012[18]	Silverman et al. 2012[17]	Möhner et al. 2013[16]
HEI (1999)[27]	*Overall view* "The data show an exposure-response relation that may be useful for quantitative risk assessment". *Limitations* (1) "The set of teamster studies may provide reasonable estimates of worker exposure to diesel exhaust, but significant further evaluation and development are needed". (2) "It cannot be established with certainty whether the causes of death used for controls adequately represent the joint distribution of exposure to diesel exhaust and smoking in the case-control study. If smoking, or diesel exhaust exposure as determined by job category, or both were associated with causes of death used for controls, results could be biased".	Not reviewed	Not reviewed	Not reviewed

B meta-analysis by Vermeulen et al. (2014)[10]

Study selection			
Search strategy	*Database*: Medline, reference lists reviews and candidate studies *Terms*: diesel, elemental carbon, lung cancer *Period*: up to April 2013		
Inclusion criteria	(1) DEE exposure expressed as cumulative EC in the exposure-response relationship (2) appropriate unexposed / low-exposed reference group (3) no major methodological shortcomings		
Studies included	Garshick et al. 2012[18] - Silverman et al. 2012[17] - Steenland et al. 1998[15]		
Studies excluded	Möhner et al. 2013 (mean cumulative exposure level was higher than almost all of the non-reference exposure categories; small number of cases; no details on derivation of the EC exposure metric; doubts about correct adjustments for previous employment in uranium mining)[16]		
Data extraction	**Steenland et al. 1998**	**Garshick et al. 2012**	**Silverman et al. 2012**
Study	Nested case-control US Trucking industry	Retrospective cohort US Trucking industry	Nested case-control US Mining industry

Exposure data	Past exposure data (estimated based on assumptions) plus exposure measurements performed in 1988-1989 (sub-micrometer EC)	Personal and work-area measurements performed in 2001-2006 (sub-micrometer EC). Also historical trends were modeled	Past exposure data (estimated) plus exposure measurements performed in 1998 -2001
Lung cancer mortality data	N = 994 cases N = 1,085 controls Period of death: 1982-1983	N= 779 lung cancer deaths Period of death: through 2000	N = 198 cases N = 562 controls
Exposure-response relationship	OR for cumulative EC exposure with a 5-year lag	HR for cumulative EC exposure with a 5-year lag Data used which excluded mechanics due to significant changes in job duties in this job category	OR for cumulative EC exposure with a 15-year lag
Input data for the primary meta-analysis	Exposure (average, range) CI, 95% confidence interval 5-year lag Reference (0, 0–0 µg/m^3-y): RR = 1.00 Cat 1 (84.5, 0-<169 µg/m^3-y): RR = 1.08 (CI 0.72-1.63) Cat 2 (231, 169–257 µg/m^3-y): RR = 1.10 (CI0.74-1.65) Cat 3 (294, 257-331 µg/m^3-y): RR = 1.36 (CI 0.90-2.04) Cat 4 (551.7, ≥331 µg/m^3-y): RR = 1.64 (CI 1.09-2.49)	Exposure (average, range) CI, 95% confidence interval 5-year lag Reference (15.5, 0-<30 µg/m^3-y): RR = 1.00 Cat 1 (51.3, 30.9-71.7 µg/m^3-y): RR = 1.31 (CI 1.01-1.71) Cat 2 (111, 71.7-150.3 µg/m^3-y): RR = 1.38 (CI1.02-1.87) Cat 3 (250.5, ≥ 150.3 µg/m^3-y): RR = 1.48 (CI 1.05-2.10)	Exposure (average, range) CI, 95% confidence interval 15-year lag All workers (underground + surface) Reference (1.5, 0-<3 µg/m^3-y): RR = 1.00 Cat 1 (37.5, 3- 72 µg/m^3-y): RR = 0.74 (CI 0.40-1.38) Cat 2 (204, 72-536 µg/m^3-y): RR = 1.54 (CI 0.74-3.20) Cat 3 (1036, ≥536 µg/m^3-y): RR = 2.83 (CI1.28-6.26)
Meta-regression			
General	Categorical RR estimates for lung cancer mortality in association with different cumulative exposure levels, relative to lowest exposure category		
Estimate cumulative exposure	Midpoint of the range per exposure category Upper exposure category: midpoint = 5/3 times the lower bound of the category; in Silverman et al., median value		
Meta-regression models	(1) Full linear model: $\ln RR = \beta_0 + \beta_1$ (exposure) + $\sigma_{u0}^2 + \sigma_{u1}^2 + \sigma_{e0}^2$ (2) Full linear model plus natural spline variable (estimated by third order polynomials to fit nonlinear slope		
Sensitivity analyses	**Steenland et al. 1998**	**Garshick et al. 2012**	**Silverman et al. 2012**
Primary analysis 1	5-year lag	5-year lag, excluding mechanics	15-year lag
Sensitivity anal. 2	5-year lag	No lag, excluding mechanics	15-year lag
Sensitivity anal. 3	5-year lag	10-yr lag, excluding mechanics	15-year lag
Sensitivity anal. 4	5-year lag	5-year lag, including mechanics	15-year lag
Sensitivity anal. 5	5-year lag	5-year lag, excluding mechanics	No lag
Sensitivity anal. 6	5-year lag	5-year lag, excluding mechanics and excluding highest exposure category(≥ 536 µg EC/m^3-years)	15-year lag
Sensitivity anal. 7	No lag	5-year lag, excluding mechanics	15-year lag
Sensitivity anal. 8	5-year lag	5-year lag, excluding mechanics	15-year lag
Sensitivity anal. 9	5-year lag	5-year lag, excluding mechanics	15-year lag

Sensitivity anal. 8+9	Including data by Möhner et al. 2013 (8) RR from original cohort analysis (9) RR adjusted for high level of EC in reference group (624 µg EC/m^3) Assumption (1): OR reference group could be adjusted upward, based on RR predicted for average exposure of (624 µg EC/m^3 (OR=2.0) Assumption (2): adjusted reference OR could be used to recalibrate non-reference effect estimates and standard errors		
Sensitivity anal. 10[43]	5-year lag	15-year lag	5 year-lag
Sensitivity anal. 11[43]	-	15-year lag	-
Sensitivity anal. 12[43]	-	15-year lag	-
Sensitivity anal. 13[43]	-	-	5 year-lag
Sensitivity anal. 14[43]	-	5-year lag; excluding mechanics	-
Results	**Estimate intercept**	**Estimate slope (β)**	
Primary analysis 1	0.0881 (95% CI -0.1423-0.3186), Pr>ItI 0.475	0.00098 (95% CI 0.0006-0.0014), Pr>ItI 0.002	
Sensitivity anal. 2	0.0673 (95% CI -0.1286-0.2633), Pr>ItI 0.520	0.00091 (95% CI 0.0005-0.0013), Pr>ItI 0.003	
Sensitivity anal. 3	0.0399 (95% CI -0.1755-0.2553), Pr>ItI 0.726	0.00102 (95% CI 0.0006-0.0015), Pr>ItI 0.002	
Sensitivity anal. 4	0.0972 (95% CI -0.1094-0.3038), Pr>ItI 0.384	0.00094 (95% CI 0.0005-0.0014), Pr>ItI 0.003	
Sensitivity anal. 5	0.1325 (95% CI -0.0879-0.3531), Pr>ItI 0.273	0.00061 (95% CI 0.0002-0.0010), Pr>ItI 0.021	
Sensitivity anal. 6	0.0765 (95% CI -0.1647-0.3178), Pr>ItI 0.554	0.00106 (95% CI 0.0004-0.0017), Pr>ItI 0.016	
Sensitivity anal. 7	0.0835 (95% CI -0.1209-0.2979), Pr>ItI 0.447	0.00093 (95% CI 0.0004-0.0014), Pr>ItI 0.007	
Sensitivity anal. 8	0.1210 (95% CI -0.1024-0.3444), Pr>ItI 0.313	0.00065 (95% CI 0.0000-0.0012), Pr>ItI 0.056	
Sensitivity anal. 9	0.1371 (95% CI -0.0677-0.3419), Pr>ItI 0.219	0.00071 (95% CI 0.0003-0.0011), Pr>ItI 0.007	
Sensitivity anal. 10[43]	-	0.00077	
Sensitivity anal. 11[43]	-	0.00106	
Sensitivity anal. 12[43]	-	0.00118	
Sensitivity anal. 13[43]	-	0.00096	
Sensitivity anal. 14[43]	-	0.00061	
Excess lifetime risk (ELR) calculation			
Method	Life-table techniques accounting for all-cause mortality $ELR = \frac{(risk_{unexposed} - risk_{exposed})}{(1 - risk_{unexposed})}$ $Risk_{unexposed}$ and $risk_{exposed}$ = estimated lifetime risks of lung cancer mortality for unexposed and exposed population (occupational exposure 20-65 years of age; 45 years) Also ELR estimated for 10 and 20 years of occupational exposure starting at the age of 20 years	*Points of departure exposure* (1) through 80 years of age (2) assumption: occupational exposure from 20 to 65 years of age (general accepted in occupational risk analysis) (3) average EC exposures of 25, 10 and 1 µg EC/m^3 (described for diesel mechanics, construction workers and professional drivers, respectively) (4) estimated average environmental EC exposure from birth to 80 years of age was 0.8 µg EC/m^3 (levels reported for metropolitan areas) (5) all exposure 5-year lags, because this lag was reported to provide the best fitting model by two of the three studies (Garshick and Silverman)	*Points of departure mortality* (1) source background all-cause mortality (both sexes) in 2009: US vital statistics CDC 2014; used to estimate probability of survival each 5-year age interval (2) source lung cancer mortality rates in 2009: US vital statistics CDC 2014; stratified by 5-year age groups; used to estimate cumulative probability of dying from lung cancer (3) all-cause and lung cancer mortality data used to estimate background lifetime risk for dying from lung cancer in absence of DEE exposure (up to age 80 years)

			(4) estimates were made for age-specific probabilities of lung cancer mortality in populations with occupational and environmental DEE exposure
Results	*Excess lifetime risks (5-year lags)* Average exposure Number of excess deaths per 10,000 individuals *Occupational exposure, 45 yrs*: 1 µg EC/m^3: ELR = 17 deaths 10 µg EC/m^3: ELR = 200 deaths 25 µg EC/m^3: ELR = 689 deaths *Occupational exposure, 20 yrs*: 1 µg EC/m^3: ELR = 8 deaths 10 µg EC/m^3: ELR = 87 deaths 25 µg EC/m^3: ELR = 252 deaths *Occupational exposure, 10 yrs*: 1 µg EC/m^3: ELR = 4 deaths 10 µg EC/m^3: ELR = 41 deaths 25 µg EC/m^3: ELR = 112 deaths *Environmental exposure, 80 yr*: 0.8 µg EC/m^3: ELR = 21 deaths	*Exposure-response curves* (1) primary model used (2) results from all sensitivity analyses, range β: - lowest β: 0.00061 (95% CI 0.00019-0.00103) - highest β: 0.00106 (95% CI 0.00040-0.00172) (3) similar estimates when data from Möhner et al. were included in meta-analysis	(1) In total 10 extracted risk estimates performed (2) Only data presented for log-linear regression models without spline variables (3) linear and spline regression models fit the data well and resulted in equivalent curves (4) cumulative exposure range, 37-1,036 µg EC/m^3-years (5) Log-linear risk models (LnRR = intercept + β x exposure): the LnRRs, estimated for 1 µg/m^3-year increase in EC for the three studies, were within a fact of 2; 95% CI overlapped largely
Estimated proportion of lung cancer deaths attributable to DEE			
Method	RR from meta-regression used for estimations attributive fraction (AF) lung cancer due to ever exposure in environmental or occupational setting in the USA and the UK (countries selected because of presence of data on proportion of population ever-exposed to DEE occupationally) *Environmental exposure:* $AF = \frac{(risk_{exposed} - risk_{unexposed})}{risk_{exposed}}$ equivalent to: AF = (RR – 1)/RR *Occupational exposure:* $AF = \frac{\Sigma_{pi}(RR_i - 1)}{[\Sigma_{pi}(RR_i - 1) + 1]}$	*Points of departure estimation AF for lung cancer mortality, environmental exposure:* (1) age 70 years (2) approximate median age lung cancer mortality in 2006-2010 (3) information on environmental exposure is limited; assumed to be on average 0.8 µg EC/m^3 for 1994-1998; corresponds with cumulative exposure at 70 years of age of 54 µg EC/m^3-years, accounting for 5-year lag (4) meta-risk function predicts an RR of 1.05 for exposed population	Estimation (1): approximately 5% of adult US and UK population has been occupationally exposed Estimation (2): 80% of exposed European workers are regarded as low-exposed workers; 20% are considered as high-exposed workers Estimation (3): average exposure in high-exposed group, 13 µg EC/m^3; in low-exposure group, 3 µg EC/m^3 (log-normal distribution, geometric SD 3.0) Estimation (4): 13 µg EC/m^3 corresponds with 585 µg EC/m^3-years of cumulative exposure (20 to 65 years, at age 70 years, using 5-year lag); 3 µg EC/m^3 with a cumulative exposure of 135 µg EC/m^3 -years

Results	AF occupational exp.: 1.3 % AF environmental exp.: 4.8% AF overall: 6% (corresponds to about 9,000 and 2,000 annual lung cancer deaths in the USA and the UK, respectively, that may be attributable to DEE exposure	*Occupational exposure* RR (3 µg EC/m^3) = 1.14 RR (13 µg EC/m^3) = 1.78 *Environmental exposure* RR (0.8 µg EC/m^3) = 1.05
Notes		
Confounding: smoking habits	Appropriate to use US lung cancer rates which are unadjusted for smoking: - smoking habits in cohorts do not differ greatly with those in the general population - if smoking does modify ELR, data from Silverman suggest higher risk for nonsmokers with high DEE exposure; since the populations of workers under study by Silverman have a lower percentage of nonsmokers than in the general population, not adjusting for smoking would imply an underestimation of the ELR	
Precision of past exposure estimates	These are far from precise and depend on broad assumptions on exposure levels and duration, however: - AF for occupational exposure is consistent with AF by Brown et al. (2012)[8] - AF for environmental exposure is generally consistent with AF by Cohen et al.(2005)[52], and Vineis et al. (2007)[53]	
Uncertainties in meta-regression analyses	(1) study data are limited resulting in uncertainty in obtained log-linear models; tests on heterogeneity were limited due small number of data points (2) Extrapolation of the results resulted in some cases in a lower exposure than observed in the studies; however, the extrapolation is not large, since exposure levels were measured as low as 1 µg EC/m^3 (3) Not al EC in the environment is from DEE (4) estimates on AF are based on broad assumptions on exposure distribution in occupational and environmental settings; available data suggest that these assumptions are limited (5) Estimates in meta-analysis differed regarding lag-times (two studies, 5-year lag, one study, 15-year lag); however sensitivity analyses revealed consistent results when for instance unlagged data were used, or a 10-year lag in one study (6) there is considerable uncertainty due to retrospective exposure assessments; however, al large number of samples were available of each study (7) The limited number of data restricted the use of models other than linear and spline curves; if nonlinear curves fit the data better, this might change the ELR and AF	
Comments by others		
Crump 2014[54]	*Exposure assessment* (1) data are inappropriately mixed from exposures lagged 5 years and 15 years. If all 5-year-lags were used the regression parameter is estimated to be 0.38 (95% CI -0.03-0.96) instead of 0.88 (95% CI 0.65-1.11; own analysis), resulting in a lower meta-regression slope, and thus in lower risk estimates. (2) The analyses did not account for a second measure of diesel exposure (exposure duration) by Garshick et al. (3) Only crude exposure summaries (e.g., midpoints of exposure intervals) were used *Reply by Vermeulen et al. 2014*[55] (1a) Optimal lag times may vary across studies, because of differences in exposure assessment, in age composition, and in extent of follow-up. Silverman et al. did not publish the analysis results on 5-year lags, although the 5-year lag model was included in the analyses. In the Silverman-study, the 5-year lag analysis showed the lowest model fit of all lags (0-25 years). Therefore it does not make sense to use this model. (1b) Indeed, the risk function may be affected by differences between lag-times. An additional sensitivity analysis using a 5-year lag model in the Silverman-study, showed that the model did not fit nearly as well as the 15-year lag model. Therefore, the 5-year model should not be used. (1c) Using the 5-year lag data from the Silverman-study in a correct way (full estimated covariance matrix), the sensitivity meta-regression analyses revealed that: a) when using the 5-year lag data from the Silverman-study, the lowest meta-regression slope is higher than reported by Crump (who used the variance estimates only), b) the lowest meta-regression slop was statistically significant (Vermeulen, 0.00065 (95% CI 0.00028-0.0010; Crump, 0.38 (95% CI -0.03-0.96)), and c) falls within all the sensitivity analyses performed in our meta-analysis.	

	(2) Adjustment for employment duration in the Garshick-study was not a second exposure measure, but appropriately reduced bias attributable to the healthy-worker survivor effect.
Crump et al. 2015[35]	*Reanalysis of the Silverman-study and suitability for quantitative risk assessment* *Reanalysis is based on:* (1) Alternative regression model: conditional logistic regression (2) inclusion adjustments for cigarette smoking as done by Silverman et al. (3) inclusion adjustments for radon exposure in underground mines (4) use of medians for each exposure quartile (such as in Silverman et al.; indicated as T1 trend), or individual estimated REC exposure (indicated as T2 trend) *Estimates exposure REC in Silverman-study is based on CO-levels, where* β *(REC~ CO$^{\beta}$) is:* DEMS_REC 1: β = 1 (used by Silverman et al. in final regression analysis) DEMS_REC 2: 5-year average CO-values (> 1976) plus ratio of Adj_HP over ventilation (< 1976); DEMS_REC 3: β = 0.58 *Alternative estimates of REC exposure by Crump et al. 2015:* REC1, β = 0.3 (same as scenario 1, except for value of β; β = 0.3 was best estimate by Crump and Van Landingham 2012) REC2, β = 0.3, excluding "High Period" in CO regression model for mine H REC3, Vermeulen et al., β = 1.0 (same as REC2, except using CO models that do not include the term "High Period" installed after 1990); data as used by Vermeulen et al. 2014 REC4, β = 0.3 (same as REC3, except for value of β), data as used by Vermeulen et al. 2014 REC5, 3-year average CO samples for post 1975 CO estimates, β = 0.3 REC6, independent of CO data, estimate REC based on any given year relative to measured REC levels in 1998-2001 *Exposure to radon (quartiles in Working Level Months (WLM); data from Silverman et al. 2012; N = cases/controls):* No exposure: N = 74 / 254, OR = 1.0 (reference) 0.0-0.6 WLM: N = 31 / 117, OR = 0.73 (95% CI 0.41-1.25) 0.6-1.9 WLM: N = 31 / 123, OR = 0.86 (95% CI 0.51-1.45) 1.9-3.0 WLM: N = 31 / 80, OR = 1.08 (95% CI 0.63-1.84) 3.0 and higher WLM: N = 31 / 92, OR = 1.32 (95% CI 0.76-2.29) *Results for all workers (N = cases / control; OR = without / with radon adjustment; CI, 95% CI)*: DEMS_REC 1: *0-3 µg/m^3-y (av 0.4 µg/m^3-y; N=49/158)*: OR = 1.00 / 1.00 (reference); *3-72 µg/m^3-y (av 20.4 µg/m^3-y; N=50/228)*: OR = 0.79 (CI 0.41-1.52) / 0.8 (CI 0.41-1.56) *72-536 µg/m^3-y (av 270.5 µg/m^3-y; N=49/157)*: OR = 1.62 (CI 0.75-3.49) / 1.33 (CI 0.59–3.00) *≥ 536 µg/m^3-y (av 1385.2 µg/m^3-y; N=50/123)*: OR = 3.24 (CI 1.40-7.55) / 2.46 (CI 0.94-6.47) *p*-trend = 0.0006 Slopes T1/T2 trends: 0.00082/0.00035 (not adjusted); 0.00064/0.00008 (adjusted) DEMS_REC 2: *0-3.4 µg/m^3-y (av 0.34 µg/m^3-y; N=49/158)*: OR = 1.00 / 1.00 (reference) *3.4-80.1 µg/m^3-y (av 23.0 µg/m^3-y; N=50/227)*: OR = 0.84 (CI 0.44-1.59) / 0.82 (CI 0.42-1.60)

80.1-457.6 µg/m³-y (*av 235.2 µg/m³-y; N=49/154)*: OR = 1.62 (CI 0.75-3.51) / 1.38 (CI 0.61–3.12)
≥ 457.6 µg/m³-y (av 1194.1 µg/m³-y; N=50/127): OR = 3.14 (CI 1.36-7.27) / 2.29 (CI 0.87-6.07)
p-trend = 0.0008
Slopes T1/T2 trends: 0.00090/0.00040 (not adjusted); 0.00063/0.00012 (adjusted)

DEMS_REC 3:
0-3.4 µg/m³-y (av 0.4 µg/m³-y; N=49/159): OR = 1.00 / 1.00 (reference)
3.4-88.8 µg/m³-y (av 24.2 µg/m³-y; N=50/225): OR = 0.85 (CI 0.44-1.61) / 0.82 (CI 0.42-1.61)
88.8-656 µg/m³-y (*av 248.7 µg/m³-y; N=49/155)*: OR = 1.77 (CI 0.83-3.78) / 1.51 (CI 0.68–3.36)
≥ 656 µg/m³-y (av 1415.3 µg/m³-y; N=50/127): OR = 3.17 (CI 1.35-7.42) / 2.35 (CI 0.85-6.52)
p-trend = 0.001
Slopes T1/T2 trends: 0.00076/0.00047(not adjusted); 0.00055/0.00009 (adjusted)

REC1:
0-6.4 µg/m³-y (av 0.8 µg/m³-y; N=49/157): OR = 1.00 / 1.00 (reference)
6.4-96.7 µg/m³-y (av 35.3 µg/m³-y; N=50/214): OR = 0.80 (CI 0.43-1.49) / 0.75 (CI 0.39-1.44)
96.7 –772.7 µg/m³-y (*av 380.2 µg/m³-y; N=49/162)*: OR = 1.58 (CI 0.73-3.41) / 1.29 (CI 0.57–2.92)
≥ 772.7 µg/m³-y (av 1782.6 µg/m³-y; N=50/133): OR = 2.49 (CI 1.06-5.85) / 1.35 (CI 0.44-4.12)
p-trend = 0.01
Slopes T1/T2 trends: 0.00047/0.00035 (not adjusted); 0.00012/0.00003 (adjusted)

REC2:
0-6.3 µg/m³-y (av 0.7 µg/m³-y; N=49/159): OR = 1.00 / 1.00 (reference)
6.3-99.2 µg/m³-y (av 32.8 µg/m³-y; N=50/217): OR = 0.75 (CI 0.39-1.44) / 0.70 (CI 0.36-1.37)
99.2-752.9 µg/m³-y (*av 385.6 µg/m³-y; N=49/167)*: OR = 1.73 (CI 0.78-3.83) / 1.47 (CI 0.63–3.44)
≥ 752.9 µg/m³-y (av 1798.5 µg/m³-y; N=50/123): OR = 3.03 (CI 1.25-7.33) / 2.04 (CI 0.67-6.24)
p-trend = 0.002
Slopes T1/T2 trends: 0.00058/0.00030 (not adjusted); 0.00035/-0.00009 (adjusted)

REC3:
0-0.6 µg/m³-y (av 0.1 µg/m³-y; N=49/194): OR = 1.00 / 1.00 (reference)
0.6-17.8 µg/m³-y (av 7.5 µg/m³-y; N=50/169): OR = 1.36 (CI 0.71-2.61) / 1.25 (CI 0.63-2.48)
17.8-224.4 µg/m³-y (*av 72.0 µg/m³-y; N=49/150)*: OR = 1.87 (CI 0.90-3.88) / 1.45 (CI 0.66–3.16)
≥ 224.4 µg/m³-y (av 1182.7 µg/m³-y; N=50/153): OR = 2.31 (CI 1.01-5.27) / 1.55 (CI 0.63-3.84)
p-trend = 0.19
Slopes T1/T2 trends: 0.00033/0.00009 (not adjusted); 0.00011/-0.00013 (adjusted)

REC4:
0-4.9 µg/m³-y (av 0.7 µg/m³-y; N=49/168): OR = 1.00 / 1.00 (reference)
4.9-70.4 µg/m³-y (av 26.7 µg/m³-y; N=50/216): OR = 0.84 (CI 0.44-1.59) / 0.80 (CI 0.41-1.55)
70.4-498.4 µg/m³-y (*av 243.3 µg/m³-y; N=49/143)*: OR = 2.12 (CI 0.98-4.58) / 1.67 (CI 0.73–3.81)
≥ 498.4 µg/m³-y (av 1522.1 µg/m³-y; N=50/139): OR = 2.45 (CI 1.05-5.76) / 1.50 (CI 0.54-4.17)
p-trend = 0.04
Slopes T1/T2 trends: 0.00041/0.00027 (not adjusted); 0.00008/-0.00008 (adjusted)

REC5:
0-7.4 µg/m³-y (av 0.8 µg/m³-y; N=49/158): OR = 1.00 / 1.00 (reference)
7.4-126.2 µg/m³-y (av 40.4 µg/m³-y; N=50/218): OR = 0.78 (CI 0.41-1.47) / 0.72 (CI 0.37-1.39)

	126.2-848.2 µg/m³-y (*av 449.0 µg/m³-y; N=49/156)*: OR = 1.78 (CI 0.80-3.93) / 1.39 (CI 0.60–3.24) ≥ *848.2 µg/m³-y (av 1994.9 µg/m³-y; N=50/134)*: OR = 2.66 (CI 1.11-6.39) / 1.52 (CI 0.50-4.56) *p*-trend = 0.01 Slopes T1/T2 trends: 0.00044/0.00026 (not adjusted); 0.00017/-0.00008 (adjusted) REC6: *0-2.8 µg/m³-y (av 0.6 µg/m³-y; N=49/181)*: OR = 1.00 / 1.00 (reference) *2.8-50.6 µg/m³-y (av 20.5 µg/m³-y; N=50/197)*: OR = 1.09 (CI 0.60-2.00) / 1.07 (CI 0.57-2.00) *50.6-388.0 µg/m³-y* (*av 158.3 µg/m³-y; N=49/157)*: OR = 1.84 (CI 0.90-3.80) / 1.35 (CI 0.62–2.94) ≥ *388.0 µg/m³-y (av 1156.9 µg/m³-y; N=50/131)*: OR = 2.56 (CI 1.10-5.90) / 1.43 (CI 0.52-3.94) *p*-trend = 0.05 Slopes T1/T2 trends: 0.00054/0.00035 (not adjusted); 0.00012/-0.000004 (adjusted) *Evaluation by HEI (2015)*[26] (1) “Of the most relevant analyses the variability was smaller, and the results still demonstrated a clear, significant association between REC exposure and lung cancer risk. The associations remained even with the alternative exposure models that did not rely on the HP-CO-REC relationships used in the original investigators’ main exposure models”. (2) The underground radon levels in the mines were very low as compared to occupational and environmental standards (1 WL (NIOSH REL, MSHA standard); 100 pCi/L (~0.5 WL, OSHA PEL); 4 pCi/L, residential indoor action level (US EPA); 4 WLM limit annual exposure (MSHA)). The mean area levels as measured in the mines ranged from 1.6 to 3.4 pCi/L, or 0.008 up to 0.017 WL (for ever underground workers). (2a) In sensitivity analyses on adjusting for radon exposure one should be aware that due to the high correlation between cumulative REC and cumulative radon exposure, adjusting for radon is essentially removing some of the effect of exposure of REC. (2b) “The low levels of radon in the mines, limited detection of and variability in the radon levels, and the inability to disentangle the cumulative REC and cumulative radon in the analyses, led the Panel to conclude that simple adjustment for cumulative exposure to radon in the Silverman-study yields results of questionable validity”. (2c) “The Panel concluded that adjustment for cumulative radon exposure was not critically important and could itself lead to unintended biases in the REC-lung cancer associations”.
Morfeld and Spallek 2015[24]	*Extended reanalysis of the meta-analysis by Vermeulen et al. 2014* *Reanalysis is based on (see also row below):* (1) alternative regression models: fixed and random effects, Greenland/Longnecker method (2) varying input data by adjusting exposure settings and accounting for confounders, such as smoking habits and radon exposure (3) including data from other studies (Möhner et al. 2013)[16] *Results and conclusion* Reanalysis showed lower relative risk estimates than those found by Vermeulen et al. 2014 in their primary and sensitivity analyses. The lowest risk estimate was found for combining data from 2b, 3b or 3c, and 4, and excluding 1a/1b (see below for explanation of numbers); “the meta-coefficient was estimated to be about 10-20% of the main effect estimated in Vermeulen et al. 2014 in this analysis”. **Vermeulen et al. 2014** *Data source:* (1) Steenland et al. 1998, 5-year lag (2) Garshick et al. 2012, 5-year lag (3) Silverman et al. 2012, 15-year lag, unadjusted for **Morfeld et al. 2015** *Data source:* (1a) Steenland et al. 1998 (1b) exclusion of Steenland et al. 1998 (2a) Garshick et al. 2012

	radon (4) exclusion of Möhner et al. 2013 *Applied regression models to assess exposure-response relationship:* (1) Full linear regression model on lnRR (inversely weighted by its variance; correlations among category specific RRs were accounted for by estimating their covariance; potential between-study heterogeneity was accounted for by allowing random study-specific intercepts and exposure effects in the regression models; with or without natural spline function	(2b) Garshick modified for duration of exposure (3a) Silverman et al. 2012, unadjusted for radon (3b) Crump et al. 2015, re-analysis of Silverman-study (REC4 model), 15-year lag, adjusted for radon exposure (3c) Crump et al. 2015, re-analysis of Silverman-study (REC6 model), 15-year lag, adjusted for radon exposure (4) Inclusion of Möhner et al. 2013, new exposure categories *Applied regression models to assess exposure-response relationship:* (A) linear regression with fixed effects on log RR with weights proportional to the inverse of respective variance; with and without adjustment by study (B) mixed linear regression for log RR with a random intercept incorporating the differences between the studies (C) mixed linear regression for log RR with a random intercept and a random dose coefficient (slope) incorporating the differences between the studies (Greenland/Longnecker method)
	Slope factors (95% confidence interval) Full linear regression (1) 0.00096 (0.00033-0.00159) (2) 0.00061 (-0.00088-0.00210) (3) 0.0012 (0.00053-0.00187) (4) not applicable (1+2+3) 0.00098 (0.00055-0.00141)	Slope factors (95% confidence interval) Linear regression with fixed effects (A) (1a) 0.00096 (0.00005-0.00187) (2a) 0.00061 (-0.00055-0.00177) (2b) 0.00005 (-0.00077-0.00087) (3a) 0.00121 (-0.00579-0.00821) (3b) 0.00033 (-0.00615-0.00680) (3c) 0.00021 (-0.00247-0.00289) (4) 0.00007 (-0.00364-0.00378) Linear regression with fixed effects, without adjusting for the studies (A): (1a+2a+3a): 0.00076 (0.00017-0.00135) (1a+2a+3b): 0.00033 (-0.00019-0.00084) (1a+2a+3c): 0.00034 (-0.00011-0.00080) Linear regression with fixed effects, with adjusting for the studies (A): (1a+2a+3a): 0.00106 (0.00057-0.00154) (1a+2a+3b): 0.00053 (0.00001-0.00105) (1a+2a+3c): 0.00054 (0.00012-0.00096) Mixed linear regression with a random intercept (B): (1a+2a+3a): 0.00097 (0.00069-0.00125) (1a+2b+3a): 0.00087 (0.00050-0.00124) (1a+2a+3b): 0.00045 (0.00003-0.00086) (1a+2b+3b): 0.00048 (0.00003-0.00092)

	(1a+2a+3c): 0.00053 (0.00002-0.00103) (1a+2b+3c): 0.00052 (0.00003-0.00101) Linear regression with fixed effects: (1b+2a+3a+4-A): 0.00054 (-0.00026-0.00133) (1b+2a+3a+4-B): 0.00024 (-0.00027-0.00074) (1b+2a+3a+4-C): 0.00032 (0.00002-0.00062) (1b+2a+3b+4-A): 0.00020 (-0.00029-0.00069) (1b+2a+3b+4-B): 0.00010 (-0.00002-0.00022) (1b+2a+3b+4-C): 0.00015 (-0.00014-0.00044) (1b+2a+3c+4-A): 0.00013 (-0.00018-0.00042) (1b+2a+3c+4-B): 0.000073 (0.00001-0.00014) (1b+2a+3c+4-C): 0.00012 (-0.00019-0.00043)

The Committee

- F.G.M. Russel, Professor of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, *chairman*
- R. Houba, Occupational Hygienist, Netherlands Expertise Centre for Occupational Respiratory Disorders, Utrecht
- E.D. Kroese, Toxicologist, TNO, Zeist
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- L.A. Smit, Epidemiologist, Institute for Risk Assessment Sciences, University Utrecht, Utrecht
- A.H. Piersma, Professor of Reproductive and Developmental Toxicology, Utrecht University, and National Institute for Public Health and the Environment, Bilthoven, *structurally consulted expert*

Observers:

- H. Stigter, Occupational Physician, Inspectorate SZW, Ministry of Social Affairs and Employment, The Hague
- D. Theodori, Social and Economic Council, The Hague

Scientific secretary:

- J.M. Rijnkels, Scientific secretary, Health Council of the Netherlands, The Hague

Consulted experts:

- P.J. Boogaard, Professor of Environmental Health and Human Biomonitoring, Wageningen University and Research Centre; and toxicologist, Shell International BV, The Hague
- R.C.H. Vermeulen, Professor of Environmental Epidemiology and Exposome Science, Institute for Risk Assessment Sciences, University Utrecht, Utrecht

With respect to the hazard assessment, the DECOS consulted two additional experts in the field of occupational epidemiology and toxicology: J. Cherrie, professor of human health, who works on exposure assessment and epidemiology (Heriot-Watt University and Institute of Occupational Medicine, the UK); and M. Van Tongeren, professor of occupational and environmental health (the University of Manchester, the UK).

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Nature and Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.
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