ÅRSBERÄTTELSE för 2017

Nordiska expertgruppen för
kriteriedokument om kemiska hälsorisker (NEG)

28 februari 2018

Gunnar Johanson, ordförande

Bakgrund

Föreliggande årsberättelse för Nordiska expertgruppen för kriteriedokument om kemiska hälsorisker (NEG) omfattar verksamhetsåret 2017. NEGs huvudsakliga uppdrag är att producera kriteriedokument på beställning av de nordiska tillsynsmyndigheterna. Dokumenten används av myndigheterna som vetenskapligt underlag för att fastställa nationella hygieniska gränsvärden för kemiska ämnen. NEG producerar även översikter som belyser det aktuella kunskapsläget om viktiga kemiska hälsorisker.

Arbetsgång

NEG beslutar efter önskemål från tillsynsmyndigheterna i Sverige, Norge, Finland och Danmark vilka dokument som ska produceras. Därefter utses en eller flera författare vars dokumentutkast diskuteras ingående när NEG sammanträder. Beslut om godkännande fattas genom konsensus.

Sekretariatet administrerar gruppens möten och håller i den löpande kontakten med ledamöter, författare samt andra samarbetspartners och organisationer. Sekretariatet utför fakta- och språkgranskning samt redigering av kriteriedokumenten och bidrar även som författare. Vidare ansvarar sekretariatet för att informera om NEGs verksamhet via gruppens hemsida, e-postutskick och genom deltagande i konferenser och dylikt.

Sammansättning

NEG består av vetenskapliga experter som representerar olika ämnesområden inom toxikologi, arbets- och miljömedicin och epidemiologi samt ett sekretariat. Under 2017 hade NEG sju ledamöter. Sekretariatet som drivs av Arbetsmiljöverket består av två vetenskapliga sekreterare samt ordföranden.

NEG-ledamöter under 2017

Experter	
Gunnar Johanson, ordf.	Professor, Institutet för miljömedicin, Karolinska Institutet, Stockholm, Sverige
Merete Drevvatne Bugge	Fil Dr, Överläkare, Statens arbeidsmiljøinstitutt, Oslo, Norge
Helge Johnsen	Fil Dr, Statens arbeidsmiljøinstitutt, Oslo, Norge
Nina Landvik	Fil Dr, Statens arbeidsmiljøinstitutt, Oslo, Norge
Helene Stockmann-Juvala	Fil Dr, Arbetshälsoinstitutet, Helsingfors, Finland
Anne Thoustrup Saber	Fil Dr, forskare, Det Nationale Forskningscenter for Arbejdsmiljø, Köpenhamn, Danmark
Mattias Öberg	Docent, senior forskare, SweTox, Södertälje, och Institutet för miljömedicin, Karolinska Institutet, Stockholm, Sverige
Vetenskapliga sekreterare	
Anna-Karin Alexandrie	Dr Med vet, Arbetsmiljöverket, Stockholm, Sverige
Jill Järnberg	Dr Med vet, Arbetsmiljöverket, Stockholm, Sverige

Finansiering

NEGs sekretariat finansierades under 2017 huvudsakligen av svenska Arbetsmiljöverket och norska Arbeids- och sosialdepartementet. Medel som utbetalas till NEG via Arbetsmiljöverket avsätts från den ordinarie budgeten medan medel via det norska departementet anvisas efter årlig begäran från Arbetsmiljöverket.

Den direkta kostnaden för NEGs verksamhet under 2017 uppgick till 1 702 447 SEK. Beloppet inkluderar lönekostnader för sekretariatet, kostnader i samband med gruppens möten samt författararvoden. Arbetsmiljöverket bidrog med 1 202 447 SEK och Arbeids- och sosialdepartementet med 500 000 NOK (~ 500 000 SEK). Därutöver står Arbetsmiljöverket för löpande kostnader som lokalhyra, kontorsmaterial och bibliotekstjänst.

Utöver detta finansieras NEG indirekt av Arbetshälsoinstitutet i Finland, Det Nationale Forskningscenter for Arbejdsmiljø i Danmark, Statens arbeidsmiljøinstitutt i Norge samt Institutet för miljömedicin i Sverige genom löne- och driftskostnader för medarbetare involverade i NEGs arbete.

Kriteriedokument och kunskapsöversikter

Kiselkarbid (Silisiumkarbid)

Kiselkarbid (SiC) används som slipmedel och eldfast material och alltmer i kompositmaterial och inom elektronikindustrin. SiC förekommer både i en fibrös och icke-fibrös form. Baserat på fysikaliska och kemiska egenskaper, morfologi och de effekter som setts i djurförsök anser NEG att den fibrösa formen ska betraktas som lika potent som asbest och den icke-fibrösa formen som ett PSLT (poorly soluble, low toxicity) damm. Dokumentet färdigställdes 2017 och publiceras inom kort; Arbete och Hälsa 2018;52(1).

Yrkesmässig hudexponering för kemikalier

Hudsjukdomar är de näst vanligaste yrkessjukdomarna i EU varav 80–90% orsakas av kemikalier. Utöver de lokala hudeffekterna kan hudexponering orsaka systemiska effekter och sensibilisering. NEGs dokument sammanfattar det aktuella kunskapsläget och beskriver möjligheter att mäta och begränsa hudexponering och därmed förekomsten av sjukdomar orsakade av hudexponering. Dokumentet godkändes 2017 och publiceras under våren; Arbete och Hälsa 2018;52(3).

Oorganiska kloraminer

Oorganiska kloraminer och i synnerhet trikloramin avges till luften när klor används för desinfektion i badhus och livsmedelsindustrin. Flera studier har visat att yrkesmässig exponering för trikloramin orsakar akuta irritationsbesvär från ögon och luftvägar och sannolikt förvärrar eller bidrar till utveckling av astma. I dagsläget saknas hygieniskt gränsvärde för trikloramin i de nordiska länderna med undantag för Finland. Dokumentet beräknas publiceras 2018.

Yrkesmässig kemisk exponering och hjärt-kärlsjukdom

Hjärt-kärlsjukdom är den vanligaste dödsorsaken i världen och det finns ökat stöd för att yrkesmässig kemisk exponering ökar risken för hjärt-kärlsjukdomar. Studier har visat att exponering för partiklar inducerar inflammation som i sin tur kan leda till hjärt-kärlsjukdom. I NEGs dokument bedöms hur starkt stödet är för att exponering för ett stort antal kemiska agens orsakar hjärt-kärlsjukdom. När data tillåter anges även den lägsta effektnivån.

Yrkesmässig kemisk exponering och ovanliga arbetstider

En betydande andel av arbetskraften har ovanliga arbetstider (mer än 8-timmar/dag, skift- eller nattarbete). I många av dessa arbetsmiljöer förekommer dessutom kemisk exponering. Långa arbetsdagar medför att den kemiska exponeringstiden ökar samtidigt som perioden för återhämtning minskar. Hygieniska gränsvärden som är baserade på 8 timmars exponering tar inte hänsyn till detta. Ovanliga arbetstider stör även dygnsrytmen vilket i sin tur kan förändra känsligheten för kemiska substanser. NEGs dokument syftar till att kartlägga hur kombinerad exponering för ovanliga arbetstider och kemikalier påverkar hälsan och riskbedömningen av kemikalier.

Yrkesmässig exponering och kroniskt obstruktiv lungsjukdom

Kroniskt obstruktiv lungsjukdom (KOL) är den fjärde vanligaste dödsorsaken i världen och kommer att vara den tredje vanligaste år 2020 om utvecklingen fortsätter i nuvarande takt. Tobaksrökning är den dominerande orsaken men yrkesmässig exponering för damm, rök och gaser beräknas svara för ca 15% av den totala sjukligheten i KOL. Betydelsen av yrkesmässig exponering har nyligen bekräftats i en svensk studie med KOL-patienter som aldrig rökt. Det finns också ökat stöd för att KOL kan förvärras av yrkesmässig exponering.

Trädamm

Enligt en stor europeisk undersökning var 58 000 arbetstagare i Sverige, 65 000 i Finland och 72 000 i Danmark yrkesmässigt exponerade för inhalerbart trädamm år 2000–2003. Av dessa var ca 30% exponerade för nivåer överstigande 2 mg/m^3, dvs över det gällande hygieniska gränsvärdet i dessa länder. Exponering för trädamm har förknippats med en rad negativa hälsoeffekter såsom luftvägs- och hudsymtom som uppträder vid relativt låga exponeringsnivåer (1 mg/m^3) och vid långvarig exponering cancer i näsan. NEGs rapport kommer att identifiera och sammanfatta litteraturen om hälsoeffekter av exponering för trädamm.

Halogener

På begäran av tillsynsmyndigheterna arbetar NEG med att ta fram ett kriteriedokument om fluor, klor och brom då nuvarande hygieniska gränsvärden behöver uppdateras.

Gränsvärdesättning av carcinogener

Ökad kunskap om carcinogener har gjort att riskbedömningen är mer diversifierad och beaktar ämnets verkningsmekanismer och relativa potens. NEGs dokument kommer att beskriva principer/metoder för riskbedöma carcinogener, diskutera hygieniska gränsvärden i relation till acceptabel risk samt ge rekommendationer hur framtagandet av hälsobaserade gränsvärden för carcinogener kan förbättras. Ett första utkast kommer att diskuteras våren 2018.

Arbete i miljöer med låga syrenivåer

Låga syrenivåer förekommer naturligt vid arbete på hög höjd, i slutna utrymmen och gruvor. I vissa fall sänker man även aktivt syrenivåerna i syfte att öka brandsäkerheten. Med anledning av det ökande antalet förfrågningar till tillsynsmyndigheterna angående dispenser för arbete i syrereducerade miljöer har NEG påbörjat ett dokument om hur låga syrenivåer påverkar hälsan och vid vilka nivåer effekterna uppträder.

Möten

Under 2017 har NEG haft 4 protokollförda möten. Vid dessa möten diskuterades 6 av de 10 ovan nämnda dokumenten. Vidare diskuterades behovet av nya kriteriedokument och förslag på författare. Dessutom lämnades rapporter från vetenskapliga kurser och konferenser samt från möten med de nordiska tillsynsmyndigheterna, internationella expertkommittéer och andra aktörer inom området.

6–7 mars, Akademihotellet, Uppsala

Ett tredje utkast av oorganiska kloraminer diskuterades och utkastet om yrkesmässig hudexponering för kemikalier godkändes med mindre revidering. Mot bakgrund av EUs ändring av carcinogen- och mutagendirektivet och deras kampanj för att minska arbetsrelaterad cancer diskuterades behovet av att skriva ett dokument om gränsvärdessättning av carcinogener. Diskussionen om att utveckla slutsatserna i framtida NEG-dokument och rekommendera hälsobaserade gränsvärden fortsatte. Likaså diskuterades arrangemanget av NEGs 40-årsjubileum 2018.

12–13 juni, Clarion Hotel Gillet, Uppsala

Reviderade utkast om oorganiska kloraminer respektive yrkesmässig kemisk exponering och ovanliga arbetstider diskuterades. NEG beslutade att skriva en synopsis för dokumentet om gränsvärdessättning av carcinogener avsedd som beslutsunderlag för de nordiska tillsynsmyndigheterna. NEG diskuterade även en inbjudan från den holländska expertgruppen DECOS om att samverka i framtagandet av kriteriedokument för ett flertal kemiska substanser. Diskussionen om plats och program för NEGs 40-årsjubileum fortsatte.

6–7 november, Akademihotellet, Uppsala

Ett reviderat utkast om yrkesmässig kemisk exponering och hjärt-kärlsjukdom respektive ett första utkast om yrkesmässig exponering och kroniskt obstruktiv lungsjukdom diskuterades. Vidare diskuterades ett norskt förslag om att skriva ett dokument om cementdamm. Det bestämdes att fråga tillsynsmyndigheterna om deras intresse för dokument om cementdamm, kvarts och om respirabelt och inhalerbart damm (de senare i samverkan med DECOS). NEG beslutade även att fortsättningsvis rekommendera hälsobaserade gränsvärden då förslaget mottagits positivt av de nordiska tillsynsmyndigheterna i samband med deras årliga möte i september 2017. Detaljer kring programmet för NEGs 40-årsjubileum som arrangeras i anslutning till arbets- och miljömedicinska klinikernas vårmöte i Linköping diskuterades.

20–21 november, Statens arbeidsmiljøinstitutt, Oslo

Reviderade utkast om oorganiska kloraminer, trädamm och om yrkesmässig kemisk exponering och ovanliga arbetstider diskuterades. Utkastet om oorganiska kloraminer som är i slutfasen bedömdes kunna godkännas via e-post/videokonferens efter utförd revidering. De beslutades att dokumentet om gränsvärdessättning av carcinogener ska skrivas efter godkännande av samtliga nordiska tillsynsmyndigheter. Tänkbara författare till dokumenten om cementdamm, arbete i miljöer med låga syrenivåer samt kemikalier och reproduktionseffekter diskuterades. Det beslutades att framöver utse en NEG-expert som mentor till varje författargrupp för att underlätta skrivandet av kriteriedokumenten.

Publicitet

Arbete och Hälsa

Samtliga NEG-dokument som producerats sedan starten 1978 har publicerats i den vetenskapliga tidskriftsserien Arbete och Hälsa som utges av Göteborgs universitet. Av den tryckta upplagan distribueras 80 ex via Göteborgs universitet till fasta prenumeranter, och ungefär lika många via NEGs sekretariat och ledamöter till nordiska och utomnordiska myndigheter och organisationer. Av miljöskäl har NEG-sekretariatets distribution av tryckta exemplar till stor del ersatts med e-postutskick.

NEGs hemsida

Samtliga dokument finns tillgängliga på NEGs (http://www.nordicexpertgroup.org), Arbetsmiljöverkets (https://www.av.se/en/the-nordic-expert-group/) och Göteborgs universitets (https://gupea.ub.gu.se/handle/2077/3194) hemsidor. Under 2015 nedladdades ca 20 000 NEG-dokument, nära en fördubbling jämfört med 2013. Data för 2016–2017 saknas på grund av tekniska problem hos utgivaren.

E-postutskick

För att synliggöra NEGs verksamhet görs e-postutskick med information om och länk till nya NEG-dokument till ca 1 000 intressenter verksamma vid nationella och internationella myndigheter och organisationer involverade i riskbedömning av kemikalier (ex. WHO/IPCS, EU SCOEL, EU LIC, ANSES, DECOS, HSE, MAK, ACGIH, AEGL, NIOSH, FHI, KEMI, KI, MSB och arbets- och miljömedicinska kliniker). E-postutskick görs också till fackpress efter behov.

Nyhetsnotiser

Sekretariatet lägger även ut nyhetsnotiser om nya NEG-dokument på Arbetsmiljöverkets och Institutet för miljömedicins hemsidor. NEGs ledamöter ansvarar för att lägga ut notiser på respektive instituts hemsidor.

Konferenser

Dokumentet om kiselkarbid (silisiumkarbid) presenterades av författaren och tillika NEG-ledamoten Merete Bugge vid *International Symposium on Fibre Morphology*, 17 november 2017 i Bochum.

NEGs ordförande var inbjuden föreläsare vid *Arbete och Hälsas 50-årsjubileum* som arrangerades av AFA försäkringar i Stockholm 30 november 2017 för att berätta om hur NEGs dokument används. Se https://www.afaforsakring.se/forskning/ovrigt/arbete-och-halsa-50-ar/.

NEGs ordförande blev även inbjuden till *Norsk Selskap for Farmakologi og Toksikologis vintermöte* 25–28 januari 2018 i Beitostølen. Föredraget med titeln ”Setting health-based occupational exposure limits” inkluderade såväl NEGs som andra expertkommittéers metodik vid framtagandet av gränsvärden. Se detaljerat program för konferensen på http://conferences.academicjournals.info/cat/medical-sciences/norwegian-society-for-pharmacology-and-toxicology-winter-meeting-2018.

En poster för dokumentet om kiselkarbid kommer att presenteras vid *Society of Toxicology*, årliga möte 11–15 mars 2018 i San Antonio (bilaga 1). Se detaljerat konferensprogram på http://www.toxicology.org/events/am/AM2018/index.asp.

NEG ska i samband med *Arbets- och Miljömedicinska klinikernas vårmöte* 25–27 april 2018 i Linköping arrangera en session med titeln Nordiska expertgruppen 40 år – Forskning blir gränsvärden. Förutom en historisk tillbakablick kommer några aktuella NEG-dokument presenteras (dieselmotoravgaser, kiselkarbid, oorganiska kloraminer och yrkesmässig kemisk exponering och hjärt-kärlsjukdom). Se Arbets- och miljömedicinbloggen om NEGs session på http://arbetsochmiljomedicin.se/nordiska-expertgruppen-pa-varmotet/ och det fullständiga konferensprogrammet på http://arbetsochmiljomedicin.se/varmotet-2018-i-linkoping-programanmalan/.

Övrig publicitet

Det kommande dokumentet om oorganiska kloraminer omtalades när NEGs ledamot Mattias Öberg intervjuades i *Tv4s Nyhetsmorgon* den 3 mars 2017. Se inslaget på http://www.tv4.se/nyhetsmorgon/klipp/kiss-i-poolen-s%C3%A5-farligt-%C3%A4r-det-3820432.

En översiktsartikel baserad på NEGs dokument om dieselmotoravgaser publicerades 2017; Piia Taxell and Tiina Santonen. Diesel engine exhaust: basis for occupational exposure limit value. *Toxicological Sciences* 2017;158(2):243–251 (bilaga 2). Artikeln finns fritt tillgänglig på https://doi.org/10.1093/toxsci/kfx110.

Samarbete och internationella kontakter

Arbetet inom NEG har fungerat bra och samarbetsklimatet har varit mycket gott. Lång tradition och hög kvalitet har gjort att NEG har ett fortsatt mycket gott renommé internationellt. Det nordiska arbetsmiljöarbetet får inflytande i EU genom att NEG-dokument används som utgångspunkt för diskussion om gränsvärden i EUs expert-kommitté SCOEL.

NEG försöker även förbättra sin relevanssäkring genom att verka för närmare kontakter med de nordiska tillsynsmyndigheterna och arbets- och miljömedicinska klinikerna och genom medverkan i och samarbete med andra internationella aktörer såsom SCOEL, DECOS, AEGL och LCI.

EUs Scientific Committee on Occupational Exposure Limits (SCOEL)

NEGs ordförande som sedan många år varit ledamot i SCOEL valdes till vice ordförande för kommittén för perioden 2015–2017. NEGs norske ledamot, Helge Johnsen, deltar i SCOELs arbete sedan 2013 som observatör. NEGs dokument (t.ex. dieselmotoravgaser) har vid ett flertal tillfällen använts som underlag/referens för SCOELs motsvarande dokument. SCOELs verksamhet beskrivs på http://ec.europa.eu/social/main.jsp?catId=148&intPageId=684&langId=en.

The Dutch Expert Committee on Occupational Safety (DECOS)

NEG har sedan många år samarbete med DECOS. Hittills har 15 dokument samproducerats och för närvarande diskuteras att skriva flera gemensamma kriteriedokument. DECOS arbete beskrivs på http://www.gezondheidsraad.nl/en/about-us/the-council/permanent-committees/dutch-expert-committee-on-occupational-safety.

Acute Exposure Guideline Levels (AEGL) committee

NEGs ordförande har under flera år ingått i AEGL-kommittén vid amerikanska National Academy of Sciences. AEGL-värden är riktvärden för akut exponering från 10 minuter till 8 timmar. Riktvärdena representerar exponeringsnivåer under vilken skadliga hälso-effekter är osannolika även hos barn och andra känsliga grupper. Finala AEGL-värden

har publicerats för 177 ämnen, samlade i 19 bokvolymer. AEGLs verksamhet beskrivs på http://www.epa.gov/aegl/.

Subgroup on EU-LCI (lowest concentration of interest) Values

NEGs ordförande ingår även i denna arbetsgrupp sedan 2011 som under 2015 etablerades som en expertgrupp inom EU-kommissionen. Gruppen utför hälsobaserad bedömning av emission av kemiska ämnen från byggnadsmaterial till inomhusluften. Arbetet syftar till en harmoniserad bedömning inom EU. Hittills har ca 110 kemiska ämnen fått ett EU-LCI-värde. Gruppens verksamhet beskrivs på http://www.eu-lci.org.

European Chemicals Agency's (ECHAs) Committee for Risk Assessment (RAC)

NEGs finländska ledamot, Helene Stockmann-Juvala, deltar vid mötena i ECHAs riskbedömningskommitté (RAC) som rådgivare åt ledamoten Tiina Santonen (fd NEG-expert). RAC utarbetar ECHAs yttranden om kemiska ämnens risker för människors hälsa och miljön under Reach- och CLP-processer. Kommitténs verksamhet beskrivs på https://echa.europa.eu/sv/about-us/who-we-are/committee-for-risk-assessment.

US Society of Toxicology (SOT)

NEGs ordförande medverkar i amerikanska SOT, främst vid det årliga mötet med cirka 7 000 deltagare och som redaktör (associate editor) för SOTs vetenskapliga tidskrift Toxicological Sciences. Vi presenterar återkommande postrar om NEGs nya dokument vid SOT. Läs mer om SOT och det årliga mötet på https://www.toxicology.org/.

Silicon carbide – fibrous forms should be considered equally potent as asbestos

Gunnar Johanson[1,3], Merete Bugge[2,3], Vidar Skaug[2,3]

[1] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden [2] National Institute of Occupational Health, Oslo, Norway [3] The Nordic Expert Group

Conclusions

- **Angular SiC** has slight inflammatory activity but generally low toxicity. Similar with other poorly soluble, low toxicity (PSLT) dusts.
- **SiC fibers** induce inflammatory, fibrogenic and carcinogenic effects in experimental animals comparable to those of amphibole asbestos fibers and should be considered equally potent in humans.

Figure 1. *Piece of crude SiC (left) and close-up (right)*

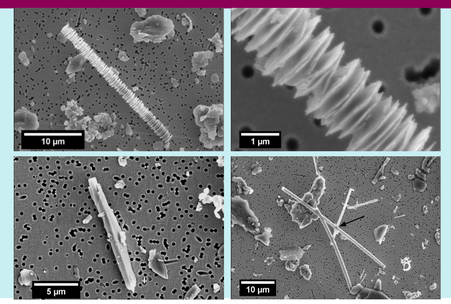


Figure 2. *SEM images of polycrystalline SiC fibers (photos by Asbjørn Skogstad).*

Figure 3. *SiC grinding wheels.*

Occurrence and use

SiC as a natural mineral is very rare, but it is manufactured industrially (figure 1) with China and Norway as the biggest producers. It may exist in several forms:

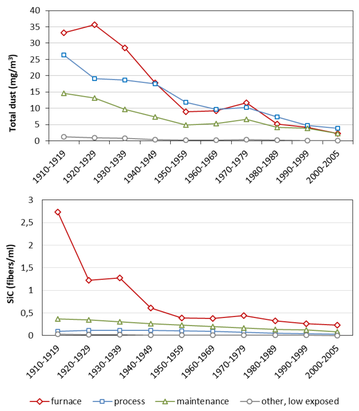
- non-fibrous = angular
- fibrous = polycrystalline fibers (figure 2) and single crystal whiskers,
- cleavage fragments,
- platelets,
- amorphous,

and in large range of particles sizes.

Angular SiC is used as abrasives and cutting devices (figure 3), in ceramic applications, heating elements, electronic devices, composites and metallurgy. Polycrystalline SiC fibers are formed unintentionally during the production of angular SiC. SiC whiskers are used for strengthening of composite materials and in electronic components. SiC nanoparticles are increasingly produced.

Exposure in SiC production

The most extensive exposure data are from the SiC production industry in Norway. Job exposure matrices showing estimated historical exposure to dust, angular SiC and SiC fibers were developed from previous and current measurements, knowledge about changes in the production, and individual employment histories, using multiple regression and mixed effect models. Figure 4 shows estimated mean exposures over 10-year time periods in different departments.



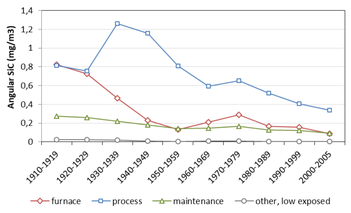


Figure 4. *Estimated exposure by department in long-term SiC production industry.*

Health effects – summary of human data

Nearly all epidemiological studies on SiC have been performed in the SiC production industry where workers were exposed to a mixture of SiC, quartz, cristobalite and other dusts, and CO and other gases (Figures 6 and 7). Adverse health outcomes in the respiratory tract are lung fibrosis, obstructive lung diseases and lung cancer. Due to the complex exposures, human data cannot be used for assessing exposure-response relationships for angular SiC and polycrystalline SiC fibers. There are no human data on the health effects of SiC whiskers.

Health effects – summary of animal data

Non-fibrous SiC: Some animal and in vitro studies indicate a slight inflammatory activity, but most studies conclude that the toxicity is low. There are no data to identify dose-response relationships. The physico-chemical properties indicate that non-fibrous SiC should be considered to be of similar toxicity as PSLT dusts.

Fibrous SiC: SiC whiskers induce inflammation and fibrosis in the lungs of rats and mice after *it* instillation and inhalation. In life-long studies with SiC whiskers, rats develop local mesotheliomas after inhalation and intrapleural and *ip* injection, in accordance with the fiber paradigm. The inflammatory, fibrogenic and carcinogenic effects observed in experimental animals exposed to SiC whiskers are comparable to those of amphibole asbestos fibers. Considering the similarities in morphology, biopersistence and effects in experimental animals, SiC whiskers and polycrystalline SiC fibers should be considered to be equally potent in humans as amphibole asbestos fibers.

The Acheson method

Angular SiC can be produced by several methods. The Acheson method is the most widely used (figure 5). It was developed around 1890 and is basically still the same. A mixture of finely ground quartz sand and petroleum coke is placed in open furnaces with removable concrete side walls and electrodes at each end.

The burning process lasts 40-170 h whilst the core reaches ≈2500°C. Above 1700°C, silicon in the quartz and carbon in the coke combine to form SiC and CO:

$$SiO_2 + 3\,C \rightarrow SiC + 2\,CO$$

Figure 5. *Acheson production of SiC.*

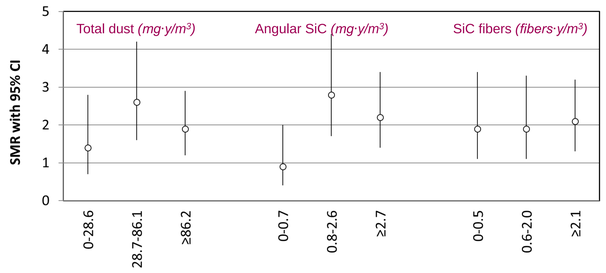


Figure 6. *Mortality from obstructive lung diseases 1951–2007 stratified by cumulative exposure among 1687 Norwegian SiC industry workers employed >3 years during 1913–2003. The SMRs were significantly increased at the two higher tertiles of exposure.*

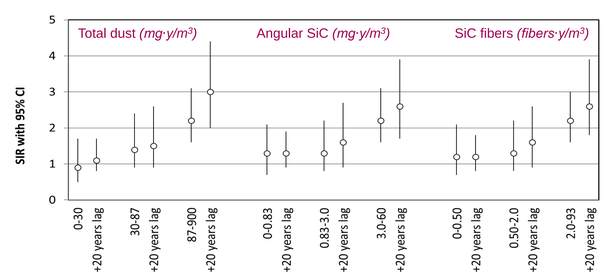


Figure 7. *Incidence of lung cancer 1953-2008 increased significantly with cumulative exposure, with and without 20 years exposure lag. However, the association with angular SiC was non-significant after including cristobalite and/or SiC fibers in the model.*

Abbreviations

CO	Carbon monoxide
ip	Intraperitoneal
it	Intratracheal
NEG	The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
OEL	Occupational Exposure Limit
PSLT	Poorly Soluble Low Toxicity (dust)
SEM	Scanning Electron Microscopy
SiC	Silicon Carbide
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio

The Nordic Expert Group

This poster is based on *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals.150. Silicon carbide. Arbete och Hälsa (in press).*

NEG's main task is to produce criteria documents to be used by regulatory authorities as the scientific basis for OELs. It consists of scientific experts from the Nordic countries representing different fields of science.

NEG is financed/supported by the Swedish Work Environment Authority, the Norwegian Ministry of Labour and Social Affairs, IMM and the National Institutes of Occupa-tional Health, in Norway, Denmark and Finland.

All documents are freely available in the scientific serial Arbete och Hälsa, download at www.nordicexpertgroup.org

Gunnar Johanson
Work Environment Toxicology
Institute of Environmental Medicine

Karolinska Institutet
Box 210
SE-171 77 Stockholm SWEDEN

gunnar.johanson@ki.se
Phone:+46 8 524 822 26
Web site: *ki.se/imm*

OXFORD
SOT | Society of Toxicology
www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 158(2), 2017, 243–251

doi: 10.1093/toxsci/kfx110
Advance Access Publication Date: June 15, 2017
Contemporary Review

CONTEMPORARY REVIEW

Diesel Engine Exhaust: Basis for Occupational Exposure Limit Value

Piia Taxell[1] and Tiina Santonen

Finnish Institute of Occupational Health, Helsinki, Finland

[1]To whom correspondence should be addressed at Finnish Institute of Occupational Health, POB 18, FI-00391 Helsinki, Finland. E-mail: piia.taxell@ttl.fi.

ABSTRACT

Diesel engines are widely used in transport and power supply, making occupational exposure to diesel exhaust common. Both human and animal studies associate exposure to diesel exhaust with inflammatory lung effects, cardiovascular effects, and an increased risk of lung cancer. The International Agency for Research on Cancer has evaluated diesel exhaust as carcinogenic to humans. Yet national or regional limit values for controlling occupational exposure to diesel exhaust are rare. In recent decades, stricter emission regulations have led to diesel technologies evolving significantly, resulting in changes in exhaust emissions and composition. These changes are also expected to influence the health effects of diesel exhaust. This review provides an overview of the current knowledge on the health effects of diesel exhaust and the influence of new diesel technologies on the health risk. It discusses the relevant exposure indicators and perspectives for setting occupational exposure limit values for diesel exhaust, and outlines directions for future research. The review is based on a collaborative evaluation report by the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Safety.

Key words: diesel engine exhaust; health effects; occupational exposure limit value; review.

Over 3.6 million workers are exposed to diesel engine exhaust (DE) in Europe (EC, 2017). Occupational exposure occurs in mining, construction work, professional driving, agriculture, and other activities that apply diesel-powered vehicles and tools. The highest exposures have been detected in underground mines and tunnel construction sites, ie, enclosed worksites that use heavy diesel equipment (Coble *et al.*, 2010; Pronk *et al.*, 2009).

In 2012, the International Agency for Research on Cancer (IARC) classified DE as carcinogenic to humans (Group 1), following evidence of a causal association between DE exposure and an increased risk of lung cancer in humans (IARC, 2013). This classification was primarily based on recent epidemiological evidence from U.S. non-metal miners (Attfield *et al.*, 2012; Silverman *et al.*, 2012). However, the epidemiological evidence of the carcinogenicity of DE comes from workers exposed to DE mainly >20 years ago. In the last two decades, tighter emission regulations in the USA, the EU and other parts of the world have caused a significant evolution in diesel technologies, resulting in changes in the emission and composition of exhaust (McClellan *et al.*, 2012).

New data on the carcinogenicity of DE and the upgrading of the IARC cancer classification from probably carcinogenic to carcinogenic, together with the high number of DE-exposed workers have emphasized the need for setting an occupational exposure limit (OEL) value for DE in many countries. Therefore, the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) and the Dutch Expert Committee on Occupational Safety (DECOS) decided to prepare a collaborative evaluation report on DE which could be used as a background document for setting OELs (Taxell and Santonen, 2016). The evaluation concerned exhaust produced by diesel engines fuelled by petroleum-based diesel fuels. It took into account the development of diesel technology and assessed the possible impact of the changes in exhaust composition on the health risks of DE. This review is based on the findings of the report.

COMPOSITION AND CHARACTERISTICS

The DE is a complex mixture of substances in the gaseous and particulate phases. The emission rate and exact composition of

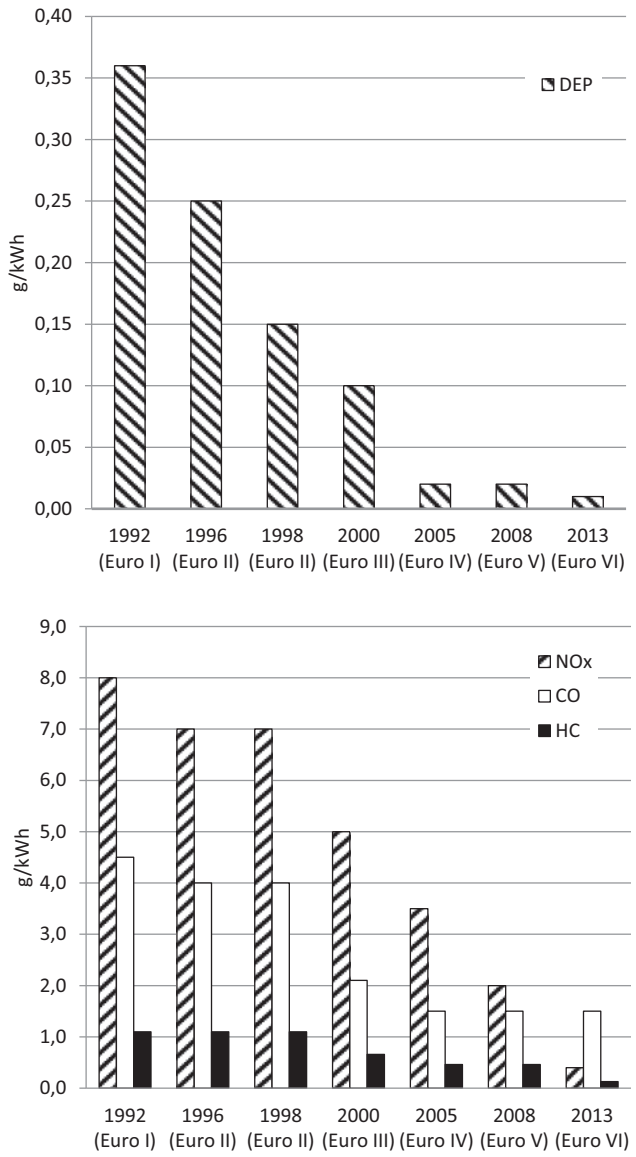


Figure 1. Development of emission standards for heavy-duty diesel engines in the EU. DEP: diesel exhaust particles, CO: carbon monoxide, HC: total hydrocarbons, NOX: nitrogen oxides. Adapted from Taxell and Santonen 2016.

the exhaust depend on the type, age, operational condition, and maintenance of the engine; on the composition and properties of the fuel; and on the exhaust after-treatment techniques applied (McDonald *et al.*, 2004, 2011).

The gaseous phase of DE contains nitrogen, carbon dioxide, oxygen, water vapor, nitrogen oxides (NO_X), carbon monoxide (CO), small amounts of sulfur dioxide (SO_2), and various organic compounds (McDonald *et al.*, 2004; USEPA, 2002). Diesel exhaust particles (DEP) contain elemental carbon (EC), organic compounds, sulfates, nitrates, and trace amounts of metals and other elements. Figure 1 presents the EU emission standards for heavy-duty diesel vehicle engines from 1992 to 2013, as an example of the significant evolution of the emission regulations seen in the last decades.

The exhaust composition of new technology diesel engines, with multi-component emission reduction systems including the diesel particulate filter and oxidation catalyst (referred to hereafter as "new technology diesel engine exhaust"), differs from that of older diesel engines. The mass of DEP emissions is reduced by more than 90% (McClellan *et al.*, 2012). The proportion of EC in the particles is reduced, and that of sulfates increased, reflecting the reduction of carbonaceous particles (Khalek *et al.*, 2011). Also, the emissions of organic compounds, such as polycyclic aromatic hydrocarbons (PAHs), aromatics, and aldehydes, are significantly reduced by new technology diesel engines (Liu *et al.*, 2010).

HEALTH EFFECTS

Most of the data available on the health effects of DE relate to older technology diesel engine models from the 1950s to the early 2000s. The following sections summarize the available human and animal data on the health effects of older and new technology DE. The key experimental findings and identified NOEALs/LOAELs (no-observed adverse effect levels/lowest observed adverse effect levels) are presented in Table 1.

Older Technology Diesel Engine Exhaust

Noncancer Effects: Animal Data

Several animal studies associate DE exposure with inflammatory effects in the lungs. Inhalation studies of rats have consistently shown that increased exposure leads to increased occurrence and severity of lung inflammatory and histopathological changes, ranging from mild alveolar septal cell hyperplasia at 210 μg DEP/m^3 to fibrotic lesions at ≥750 μg DEP/m^3, and lung tumors at ≥2 200 μg DEP/m^3 after 104–130 weeks of exposure (Brightwell *et al.*, 1986; Heinrich *et al.*, 1995; Kato *et al.*, 2000; Nikula *et al.*, 1995).

In addition to lung inflammation, some animal studies associate DE exposure with other health effects, although the datasets are less comprehensive. Two studies applying susceptible animal models associate DE exposure with an exacerbation of atherosclerosis at 200 or 1000 μg DEP/m^3 (Bai *et al.*, 2011; Campen *et al.*, 2010). Changes in cardiac function have also been reported, but without a clear dose response (Carll *et al.*, 2012; Lamb *et al.*, 2012).

Other animal studies suggest that DE may have an adjuvant allergenic effect. For example, an increase in ovalbumin-induced lung inflammation was reported in mice concurrently exposed to DE at 170 μg DEP/m^3 (0.5 ppm NO_2), or a corresponding concentration of particle-free exhaust for 8 weeks (Tanaka *et al.*, 2013). The same did not occur, however, in mice exposed to 100 μg DEP/m^3 (2.2 ppm NO_2) for 12 weeks (Matsumoto *et al.*, 2006).

The DE has also been suspected of causing neurological effects. The Morris water maze test showed that the learning performance of female mice exposed to DE at 120 μg DEP/m^3 (0.5 ppm NO_2; 2.8 ppm CO) for 13 weeks decreased (Win-Shwe *et al.*, 2012). However, no effect on learning performance was observed in male mice exposed to DE at 150 μg DEP/m^3 (0.5 ppm NO_2; 3.3 ppm CO) for 4 weeks (Win-Shwe *et al.*, 2008). An increase in the levels of inflammatory cytokines in different regions of the brain, with no constant pattern, was found in rats exposed to ≥170 μg DEP/m^3 (Gerlofs-Nijland *et al.*, 2010; Levesque *et al.*, 2011).

A few studies suggest that DE exposure may have an impact on sperm production and testicular morphology in rodents exposed *in utero* or during adult life (eg, Ono *et al.*, 2007, 2008; Yoshida *et al.*, 1999). Dose-dependent decreases in daily sperm production and degenerative changes in seminiferous tubules were reported in adult mice, but not in rats, exposed to DE

Table 1. Key Experimental Data on Health Effects and Dose–Responses of Diesel Exhaust (Adapted From Taxell and Santonen, 2016)

Endpoint and Type of Study	New Technology Diesel Engines	Older Technology Diesel Engines	
	With Exhaust After Treatment[a]	With Particle Filter/Trap	Without Exhaust After Treatment
Human inhalation studies (1–2 h)			
Inflammatory changes in BAL/BW, increased airway resistance	No data identified	No data identified	LOAEL: 100 μg DEP/m^3 (0.2–0.4 ppm NO_2)
Sensory irritation	No data identified	No data identified	LOAEL: 100–300 μg DEP/m^3 (0.2–1.3 ppm NO_2)
Reduced response to vasodilators	No data identified	NOAEL: 3.4 ppm NO_2 (7 μg DEP/m^3)	LOAEL: 250–350 μg DEP/m^3 (0.2–1.6 ppm NO_2)
Increased ischemic burden	No data identified	No data identified	LOAEL: 300 μg DEP/m^3 (1.0 ppm NO_2)[b]
Animal inhalation studies			
Histopathological changes in lungs (104–130 week, rat)	NOAEL: 0.9 ppm NO_2 (5 μg DEP/m^3); LOAEL: 4.2 ppm NO_2 (12 μg DEP/m^3)	LOAEL: 1.1 ppm NO_2 (10 μg DEP/m^3)	LOAEL: 210 μg DEP/m^3 (0.2 ppm NO_2)
Mild decrease in pulmonary function (104–130 week, rat)	NOAEL: 0.9 ppm NO_2 (5 μg DEP/m^3); LOAEL: 4.2 ppm NO_2 (12 μg DEP/m^3)	No data identified	NOAEL: 2 000 μg DEP/m^3 (1.5 ppm NO_2) LOAEL: 3 500 μg DEP/m^3 (0.3 ppm NO_2)
Lung tumors (104–130 week, rat)	NOAEL: 4.2 ppm NO_2 (12 μg DEP/m^3)	No lung tumors (original conc. 6 600 μg DEP/m^3, no data on final exposure levels)	NOAEL: 800–1 000 μg DEP/m^3 (0.3 ppm NO_2) LOAEL: 2 200 μg DEP/m^3 (approximately 1 ppm NO_2)
DNA damage in lungs	Negative (comet)	No data identified	Positive (induction of 8-OHdG, *gpt*, and *lacI* point mutations, DNA strand breaks and adducts)
Systemic genotoxicity	Negative (8-OHdG, micronuclei)	No data identified	Mostly negative
In vitro studies			
Genotoxicity	No data identified	Mutagenic to bacteria (limited data)	Mutagenic to bacteria and mammalian cells (DEP extracts)

[a]US 2007 compliant heavy-duty engine.
[b]Stable coronary heart artery disease.
BAL, bronchoalveolar lavage; BW, bronchial wash; DEP, diesel exhaust particles; 8-OHdG, 8-hydroxydeoxyguanosine; L/NOAEL, lowest/no observed adverse effect level.

at ≥300 DEP/m^3 for 26–35 weeks (Tsukue *et al.*, 2001; Yoshida *et al.*, 1999). Developmental effects, such as decreased fetal weight gain and impaired motor coordination have occurred in some animal studies, mainly at high exposure levels (≥1000 μg DEP/m^3) (eg, Ono *et al.*, 2007; Yokota *et al.*, 2013).

Noncancer Effects: Human Data

Several short-term controlled human exposure studies (1–2 h) have focused mainly on the acute pulmonary and cardiovascular effects of older technology DE.

The gaseous phase of DE contains several irritating constituents such as NO_2 and aldehydes. Some healthy volunteers, exposed to DE at 100 μg DEP/m^3 (0.2 ppm NO_2, 0.04 mg/m^3 formaldehyde) for 2 h, reported an unpleasant odor and mild nasal, throat and eye irritation (Mudway *et al.*, 2004). Redness, secretion, and swelling in the nose and eyes were observed at 300 μg DEP/m^3 (1.3 ppm NO_2, 0.4 mg/m^3 formaldehyde) (Wierzbicka *et al.*, 2014).

Increased numbers of neutrophils and inflammatory cytokines in bronchial wash, and slightly increased airway resistance were observed in healthy volunteers at 100 μg DEP/m^3 (0.2–0.4 ppm NO_2), indicating an acute bronchial inflammatory response (Behndig *et al.*, 2006, 2011; Mudway *et al.*, 2004; Stenfors *et al.*, 2004). In asthmatic volunteers, increased bronchial hyper-responsiveness and a decline in forced expiratory volume (FEV_1) were seen after exposure at 300 μg DEP/m^3 (0.2–1.2 ppm NO_2) (Hussain *et al.*, 2012; Nordenhall *et al.*, 2001). These effects were, however, absent at 100 μg DEP/m^3 (≤0.4 ppm NO_2) (Behndig *et al.*, 2011; Riedl *et al.*, 2012; Stenfors *et al.*, 2004).

A nasal challenge with 300 μg of DEP prior to or concurrent with an allergen has been reported to enhance sensitization and allergic response (Bastain *et al.*, 2003; Diaz-Sanchez *et al.*, 1997, 1999). An accompanying challenge with cat allergen, however, produced no significant impact on immunological markers in the sputum of mildly asthmatic subjects exposed to DE by inhalation at 100 μg DEP/m^3 (0.4 ppm NO_2) (Riedl *et al.*, 2012).

A reduced response to vasodilators was observed in healthy volunteers after exposure to DE at 250–350 μg DEP/m^3 (0.2–0.9 ppm NO_2) (Barath *et al.*, 2010; Lucking *et al.*, 2011; Mills *et al.*, 2011). The effect was absent when particle-free exhaust was used. Some studies have also reported a slight decrease in brachial artery diameter and a transient increase in arterial stiffness (Lundback *et al.*, 2009; Peretz *et al.*, 2008; Tong *et al.*, 2014). During exposure to 300 μg DEP/m^3 (1.0 ppm NO_2) ST-segment depression and ischemic burden increased in subjects with stable coronary artery disease (Mills *et al.*, 2007).

Genotoxicity and Carcinogenicity in Animals and Experimental Systems

A number of studies exist on the genotoxicity of older technology DE in either *in vitro* systems or *in vivo*. Organic extracts of DEP have shown consistent mutagenic responses in bacterial cells, the highest responses usually with no metabolic activation (IARC, 1989, 2013). The mutagenicity of DEP extracts has mainly been attributed to nitroarenes (Nakagawa *et al.*, 1983;

Rivedal *et al.*, 2003; Salmeen *et al.*, 1982; Tokiwa and Ohnishi, 1986). In mammalian cells, the induction of sister chromatid exchanges, micronuclei, hypoxanthine phosphorybosyl transferase, thymidine kinase locus mutations, and DNA strand breaks has been demonstrated (IARC, 1989, 2013). Some studies have also shown mutagenic responses in bacterial cells after exposure to the gaseous or semivolatile fractions of DE (Bagley *et al.*, 1993; IARC, 1989, 2013; Westerholm *et al.*, 1991).

In *in vivo* systems, DEP and DEP extracts have also shown consistent genotoxic responses after oral, intraperitoneal or intratracheal administration (IARC, 2013). Inhalation of DE has resulted in local genotoxic damage; increases have been seen in DNA strand breaks, DNA adducts and in oxidative DNA damage in rodent lungs, and in gpt and lacI mutations in the lungs of transgenic rats and mice (Dybdahl *et al.*, 2004; Hashimoto *et al.*, 2007; Iwai *et al.*, 2000; Sato *et al.*, 2000). Systemic genotoxic responses after inhalation exposure to DE have rarely been observed; bone marrow and peripheral blood cell micronucleus, SCE and chromosomal aberration tests have mostly been negative (Morimoto *et al.*, 1986; Ong *et al.*, 1985; Pereira, 1982; Pereira *et al.*, 1981; Mauderly *et al.*, 1994). Oxidative stress, measured as free 8-OH-dG in serum, was increased dose-dependently after 1–7 days exposure to conventional DE. A slight increase also occurred after exposure to DE treated with selective catalytic reduction (Tsukue *et al.*, 2010).

Several studies have observed a statistically significant increase in lung tumor incidence in rats exposed to DE at concentrations of $\geq$2 200 μg DEP/m^3 for 104–130 weeks, associated with reduced particle clearance (lung overloading) and related inflammatory cascade (eg, Brightwell *et al.*, 1986; Heinrich *et al.*, 1995; Nikula *et al.*, 1995; Stinn *et al.*, 2005). These studies detected no indication of carcinogenicity in other organs. No effect on lung tumor incidence was observed in rats exposed to either filtered (particle-free) DE or whole DE at $\leq$800 μg DEP/m^3. No clear evidence of carcinogenicity was found in mice or hamsters, even at high-particle loads (Brightwell *et al.*, 1986; Heinrich *et al.*, 1986, 1995).

Genotoxicity and Carcinogenicity in Humans

In contrast to animal studies, which only detected carcinogenicity at high exposure levels, recent epidemiological studies link exposure to DE to an increased lung cancer risk at relatively low (occupationally relevant) cumulative exposures. A large cohort study and a nested case–control study among the U.S. nonmetal miners demonstrated an association between retrospective estimates of cumulative respirable EC exposure and lung cancer mortality (Attfield *et al.*, 2012; Silverman *et al.*, 2012). Correspondingly, cohort and case–control studies in the U.S. trucking industry detected an increase in lung cancer mortality with cumulative respirable EC exposure (Garshick *et al.*, 2008; Steenland *et al.*, 1998).

Based on three epidemiological studies providing dose-response data for DE exposure-related lung cancer mortality (Garshick *et al.*, 2008; Silverman *et al.*, 2012; Steenland *et al.*, 1998) and a log–linear meta-regression model, the estimated relationship between the relative risk (RR) of lung cancer mortality and cumulative EC exposure was ln RR = 0.00098×μg EC/m^3-year (95% confidence interval: 0.00055–0.0014×μg EC/m^3-year) (Vermeulen *et al.*, 2014). Based on this equation, 45 years of occupational exposure to DE at 1, 10, and 25 μg EC/m^3 would result in 17, 200, and 689 extra lung cancer deaths per 10 000, respectively, by the age of 80 years.

A few studies suggest genotoxic effects in the blood lymphocytes of DE exposed miners, tunnel workers, or car mechanics (Knudsen *et al.*, 2005; Osterholm *et al.*, 1995; Schoket *et al.*, 1999; Villarini *et al.*, 2008). Several studies have also been performed on bus and taxi drivers or traffic police exposed to urban air polluted with diesel and gasoline exhaust (IARC, 2013). Although DE may play a role in the genotoxic effects observed in these studies, due to the mixed exposure, an association with DE exposure cannot be confirmed.

New Technology Diesel Engine Exhaust

No human studies related to the health effects of new technology DE were found. Moreover, the data on the effects of new technology DE in animals are still rather limited.

Noncancer effects. A long-term inhalation study detected mild bronchoalveolar epithelial hyperplasia, mild fibrotic lesions, and a mild progressive decrease in pulmonary function in rats exposed to exhaust from a diesel engine compliant with the U.S. 2007 emission standards at 4.2 ppm NO_2 (12 μg DEP/m^3) (McDonald *et al.*, 2015). The findings were largely associated with NO_2.

The same study reported slight changes in three inflammation- and thrombosis-related plasma markers in female rats (Conklin *et al.*, 2015). No changes were observed in most of the studied plasma markers or in cardiovascular histopathology.

Genotoxicity and carcinogenicity. As part of the above-mentioned study, the induction of DNA damage (comet assay) in the lungs, 8-OHdG in serum and micronuclei in peripheral blood were evaluated after short- and long-term inhalation exposure. No induction of DNA damage was observed in the lungs (Bemis *et al.*, 2015; Hallberg *et al.*, 2015). In accordance with most of the studies on older technology DE, systemic genotoxicity also remained negative.

The long-term inhalation study on rats gave no indication of tumor development at doses of up to 4.2 ppm NO_2 (12 μg DEP/m^3) (McDonald *et al.*, 2015).

Mechanistic Considerations

A major mechanism postulated for the noncancer respiratory effects of DE is the DEP-associated induction of reactive oxygen species and oxidative stress, and a subsequent inflammatory response in the lungs (Li *et al.*, 2008; Ma and Ma, 2002). Of the gaseous phase constituents, NO_2 is a strong oxidant that reacts with biomolecules on cell membranes in the lower respiratory tract, causing the formation of further reactive products and oxidative stress (WHO, 1997). It is also suggested that DEP-induced oxidative stress plays a role in cardiovascular effects at multiple stages, eg, in promoting systemic inflammation, stimulating vasoconstriction and promoting atherosclerotic plaque instability (Miller *et al.*, 2012).

The mechanisms of DE-related lung cancer are likely to be multi-factorial. In rats, lung overloading is likely to play a significant role in the development of cancer after high DEP exposures. It is well known that the rat is highly sensitive to developing cancer due to lung overloading, and this effect has been demonstrated with several poorly soluble, low toxicity particles, which have not shown increased cancer risk in humans (Borm *et al.*, 2004). Lung overloading is considered an unlikely cause of the increased cancer risk seen in the epidemiological studies.

The DEP and DEP extracts have shown mutagenic/genotoxic responses both *in vitro* and *in vivo*. Although filtered DE has not

resulted in cancer in animals, the gaseous/semivolatile phase of DE is known to also contain genotoxic components. In humans, elevated levels of urinary 1-hydroxypyrene (marker for PAH exposure) and DNA adducts in lymphocytes after exposure to DE show that genotoxic components of DE are bioavailable in humans (Hemminki *et al.*, 1994; Hou *et al.*, 1995; Kuusimäki *et al.*, 2004; Nielsen *et al.*, 1996; Schoket *et al.*, 1999). In addition to direct genotoxicity, exposure to DEP and DE has resulted in inflammatory reactions, the generation of reactive oxygen/nitrogen species and oxidative DNA damage (Ichinose *et al.*, 1997; Iwai *et al.*, 2000; Nagashima *et al.*, 1995; Sagai *et al.*, 1993; Salvi *et al.*, 1999). Thus, it can be hypothesized that in addition to the direct genotoxicity caused by mutagens bound to DEP or present in the gaseous phase, the induction of chronic inflammation and oxidative stress may contribute to genotoxicity, cell proliferation and finally to lung carcinogenesis in humans.

PERSPECTIVES FOR SETTING OEL VALUES

Based on the available data, the critical health effects of DE are pulmonary inflammation and lung cancer. For older technology diesel engines, these effects are mainly associated with the particulate fraction of the exhaust, making DEP a good exposure indicator candidate. As it is challenging to distinguish between DEP and other respirable dust at workplaces, respirable EC may be applied as a marker for DEP (Birch and Cary, 1996). The EC typically constitutes around 75% of the DEP mass of older technology heavy-duty diesel engines (USEPA, 2002).

In human volunteers, slight increases in airway resistance and pulmonary inflammatory markers were observed after 1–2 h exposure to 100 μg DEP/m^3 (approximately 75 μg EC/m^3, 0.2–0.4 ppm NO_2) (Behndig *et al.*, 2006, 2011; Mudway *et al.*, 2004; Stenfors *et al.*, 2004). This represents the lowest observed (adverse) effect level (LO(A)EL) for pulmonary inflammatory response to older technology DE. No NOAEL was identified. It should, however, be noted that these data relate to short exposure periods only.

Long-term inhalation studies on rats detected mild inflammatory and histopathological changes in the lungs at 210 μg DEP/m^3 (approximately 160 μg EC/m^3, 0.2 ppm NO_2) (Ishihara and Kagawa, 2003; Kato *et al.*, 2000). No NOAEL was identified.

As regards the carcinogenicity of DE, inflammatory changes caused by extensive particle load may play a significant role in the lung tumor development seen at high doses in rats. Because the relevance of this type of pathway in humans is questionable, the use of high-dose rat studies for human cancer risk assessment is not considered appropriate.

The body of epidemiological evidence linking occupational exposure to DE with increased lung cancer risk at even relatively low exposure levels is increasing. Based on the available epidemiological studies that provide dose–response data the relationship between the RR of lung cancer mortality and cumulative EC exposure was ln $RR = 0.00098 \times \mu g\,EC/m^3$-year, corresponding to 200 extra lung cancer deaths per 10 000 for career-long occupational exposure at 10 μg EC/m^3 (Vermeulen *et al.*, 2014).

Because the mechanisms of lung cancer in humans are likely to be multifactorial, including direct genotoxicity, DEP-induced oxidative stress and pulmonary inflammation, it is currently not possible to identify a threshold level for carcinogenicity. Therefore, it is proposed that the OEL for DE be based on the cancer risk level calculated on the basis of recent epidemiological evidence. In addition, when the pulmonary inflammatory response seen in controlled human studies after 1–2 h exposure at 100 μg DEP/m^3 (approximately 75 μg EC/m^3) is taken into account, the OEL should be well below this level.

The sparse data available link high exposure to new technology DE with pulmonary inflammatory effects, without indicating genotoxicity or carcinogenicity (Bemis *et al.*, 2015; Hallberg *et al.*, 2015). In the long-term rat inhalation study, the LOAEL for inflammatory and histopathological changes in the lungs was 4.2 ppm NO_2 (12 μg DEP/m^3, approximately 3 μg EC/m^3) and the NOAEL was 0.9 ppm NO_2 (5 μg DEP/m^3, approximately 1 μg EC/m^3) (McDonald *et al.*, 2015). The observed effects were mainly associated with NO_2, making NO_2 a good exposure indicator candidate for new technology DE.

Because the emissions of DEP and the DEP-associated genotoxic compounds of new technology diesel engines are significantly lower than those of older technology diesel engines, the cancer risk (per kWh) is expected to decrease with new diesel technology. This is supported by the negative findings of the carcinogenicity study on rats (McDonald *et al.*, 2015) and the available (although limited) *in vivo* genotoxicity data (Bemis *et al.*, 2015; Hallberg *et al.*, 2015).

As the age and type of the engines and exhaust aftertreatment systems applied vary within and between workplaces, it may be appropriate to set an OEL value for DE as both respirable EC and NO_2. Neither of these values should be exceeded at workplaces where diesel engines are applied.

FUTURE DIRECTIONS

Numerous studies have been published on the health effects of DE. However, except for one set of valid animal inhalation studies, all the identified studies applied older technology diesel engines, from the 1950s to the early 2000s. Studies allowing the comparison of old and new technology DE with respect to different endpoints, including genotoxicity and inflammatory effects, would be of specific interest in the future. For example, the exceptionally wide set of human inhalation studies could be complemented by corresponding studies on new technology DE. An additional focus of further studies could be the impact of the substitution and blending of petroleum-derived diesel fuels with different type of biofuels on the composition and health effects of DE.

Further studies on the relevant exposure indicators for new technology DE, including consideration of the particle size distribution and different particle exposure metrics (eg, number vs mass concentration) would be valuable. In addition, it would be relevant to compare the hazard per mass unit of DEP from new and older technology diesel engines. Further information is also needed on actual exposure levels at workplaces that use new technology diesel engines. Updating epidemiological studies in the forthcoming decades is essential for assessing potential changes in the cancer risk.

ACKNOWLEDGMENTS

The authors would like to thank the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) and the Dutch Expert Committee on Occupational Safety (DECOS) for the fruitful collaboration.

FUNDING

This study was financially supported by Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG), which is financed by the Swedish Work

Environment Authority and the Norwegian Ministry of Labour and Social Affairs.

REFERENCES

Attfield, M. D., Schleiff, P. L., Lubin, J. H., Blair, A., Stewart, P. A., Vermeulen, R., Coble, J. B., and Silverman, D. T. (2012). The diesel exhaust in miners study: A cohort mortality study with emphasis on lung cancer. *J. Natl. Cancer Inst.* **104**, 869–883.

Bagley, S. T., Gratz, L. D., Leddy, D. G., and Johnson, J. H. (1993). Characterization of particle- and vapor-phase organic fraction emissions from a heavy-duty diesel engine equipped with a particle trap and regeneration controls. *Res. Rep. Health Eff. Inst.* **56**, 1–121; discussion 123–135.

Bai, N., Kido, T., Suzuki, H., Yang, G., Kavanagh, T. J., Kaufman, J. D., Rosenfeld, M. E., van Breemen, C., and Eeden, S. F. (2011). Changes in atherosclerotic plaques induced by inhalation of diesel exhaust. *Atherosclerosis* **216**, 299–306.

Barath, S., Mills, N. L., Lundback, M., Tornqvist, H., Lucking, A. J., Langrish, J. P., Soderberg, S., Boman, C., Westerholm, R., Londahl, J., *et al.* (2010). Impaired vascular function after exposure to diesel exhaust generated at urban transient running conditions. *Particle Fibre Toxicol.* **7**, 1–11.

Bastain, T. M., Gilliland, F. D., Li, Y. F., Saxon, A., and Diaz-Sanchez, D. (2003). Intraindividual reproducibility of nasal allergic responses to diesel exhaust particles indicates a susceptible phenotype. *Clin. Immunol.* **109**, 130–136.

Behndig, A. F., Larsson, N., Brown, J. L., Stenfors, N., Helleday, R., Duggan, S. T., Dove, R. E., Wilson, S. J., Sandstrom, T., Kelly, F. J., *et al.* (2011). Proinflammatory doses of diesel exhaust in healthy subjects fail to elicit equivalent or augmented airway inflammation in subjects with asthma. *Thorax* **66**, 12–19.

Behndig, A. F., Mudway, I. S., Brown, J. L., Stenfors, N., Helleday, R., Duggan, S. T., Wilson, S. J., Boman, C., Cassee, F. R., Frew, A. J., *et al.* (2006). Airway antioxidant and inflammatory responses to diesel exhaust exposure in healthy humans. *Eur. Respir. J.* **27**, 359–365.

Bemis, J. C., Torous, D. K., Dertinger, S. D., and Committee, H. E. I. H. R. (2015). Part 2. Assessment of micronucleus formation in rats after chronic exposure to new-technology diesel exhaust in the ACES bioassay. *Res. Rep. Health Eff. Inst.* **184**, 69–82; discussion 141–71.

Birch, M. E., and Cary, R. A. (1996). Elemental carbon-based method for monitoring occupational exposures to particulate diesel exhaust. *Aerosol. Sci. Tech.* **25**, 221–241.

Borm, P. J., Schins, R. P., and Albrecht, C. (2004). Inhaled particles and lung cancer, Part B: Paradigms and risk assessment. *Int. J. Cancer* **110**, 3–14.

Brightwell, J., Fouillet, X., and Cassano-Zoppi, A. L. (1986). Neoplastic and functional changes in rodents after chronic inhalation of engine exhaust emissions. Tsukuba Science City, Japan, pp. 471–485.

Campen, M. J., Lund, A. K., Knuckles, T. L., Conklin, D. J., Bishop, B., Young, D., Seilkop, S., Seagrave, J., Reed, M. D., and McDonald, J. D. (2010). Inhaled diesel emissions alter atherosclerotic plaque composition in ApoE(-/-) mice. *Toxicol. Appl. Pharmacol.* **242**, 310–317.

Carll, A. P., Hazari, M. S., Perez, C. M., Krantz, Q. T., King, C. J., Winsett, D. W., Costa, D. L., and Farraj, A. K. (2012). Whole and particle-free diesel exhausts differentially affect cardiac electrophysiology, blood pressure, and autonomic balance in heart failure-prone rats. *Toxicol. Sci.* **128**, 490–499.

Coble, J. B., Stewart, P. A., Vermeulen, R., Yereb, D., Stanevich, R., Blair, A., Silverman, D. T., and Attfield, M. (2010). The diesel exhaust in miners study: II. Exposure monitoring surveys and development of exposure groups. *Ann. Occup. Hyg.* **54**, 747–761.

Conklin, D. J., Kong, M., and Committee, H. E. I. H. R. (2015). Part 4. Assessment of plasma markers and cardiovascular responses in rats after chronic exposure to new-technology diesel exhaust in the ACES bioassay. *Res. Rep. Health Eff. Inst.* **184**, 111–139; discussion 141–171.

Diaz-Sanchez, D., Garcia, M. P., Wang, M., Jyrala, M., and Saxon, A. (1999). Nasal challenge with diesel exhaust particles can induce sensitization to a neoallergen in the human mucosa. *J. Allergy Clin. Immunol.* **104**, 1183–1188.

Diaz-Sanchez, D., Tsien, A., Fleming, J., and Saxon, A. (1997). Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. *J. Immunol.* **158**, 2406–2413.

Dybdahl, M., Risom, L., Bornholdt, J., Autrup, H., Loft, S., and Wallin, H. (2004). Inflammatory and genotoxic effects of diesel particles in vitro and in vivo. *Mutat. Res.* **562**, 119–131.

EC. (2007). Commission staff working document. Impact assessment. Accompanying the document Proposal for a Directive of the European Parliament and of the Council amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. European Commission, Brussels.

Garshick, E., Laden, F., Hart, J. E., Rosner, B., Davis, M. E., Eisen, E. A., and Smith, T. J. (2008). Lung cancer and vehicle exhaust in trucking industry workers. *Environ. Health Perspect.* **116**, 1327–1332.

Gerlofs-Nijland, M. E., van Berlo, D., Cassee, F. R., Schins, R. P., Wang, K., and Campbell, A. (2010). Effect of prolonged exposure to diesel engine exhaust on proinflammatory markers in different regions of the rat brain. *Particle Fibre Toxicol.* **7**, 1–10.

Hallberg, L. M., Ward, J. B., Hernandez, C., Ameredes, B. T., Wickliffe, J. K., and Committee, H. E. I. H. R. (2015). Part 3. Assessment of genotoxicity and oxidative damage in rats after chronic exposure to new-technology diesel exhaust in the ACES bioassay. *Res. Rep. Health Eff. Inst.* **184**, 87–105; discussion 141–171.

Hashimoto, A. H., Amanuma, K., Hiyoshi, K., Sugawara, Y., Goto, S., Yanagisawa, R., Takano, H., Masumura, K., Nohmi, T., and Aoki, Y. (2007). Mutations in the lungs of gpt delta transgenic mice following inhalation of diesel exhaust. *Environ. Mol. Mutagen* **48**, 682–693.

Heinrich, U., Fuhst, R., Rittinghausen, S., Creutzenberg, O., Bellmann, B., Koch, W., and Levsen, K. (1995). Chronic inhalation exposure of Wistar rats and 2 different strains of mice to diesel-engine exhaust, carbon-black, and titanium-dioxide. *Inhal. Toxicol.* **7**, 533–556.

Heinrich, U., Muhle, H., Takenaka, S., Ernst, H., Fuhst, R., Mohr, U., Pott, F., and Stober, W. (1986). Chronic effects on the respiratory tract of hamsters, mice and rats after long-term inhalation of high concentrations of filtered and unfiltered diesel engine emissions. *J. Appl. Toxicol.* **6**, 383–395.

Hemminki, K., Söderling, J., Ericson, P., Norbeck, H. E., and Segerbäck, D. (1994). DNA adducts among personnel servicing and loading diesel vehicles. *Carcinogenesis* **15**, 767–769.

Hou, S. M., Lambert, B., and Hemminki, K. (1995). Relationship between HPRT mutant frequency, aromatic DNA adducts and genotypes for GSTM1 and NAT2 in bus maintenance workers. *Carcinogenesis* **16**, 1913–1917.

Hussain, S., Laumbach, R., Coleman, J., Youssef, H., Kelly-McNeil, K., Ohman-Strickland, P., Zhang, J., and Kipen, H. (2012). Controlled exposure to diesel exhaust causes increased nitrite in exhaled breath condensate among subjects with asthma. *J. Occup. Environ. Med.* **54**, 1186–1191.

IARC. (1989). Diesel and gasoline engine exhaust and some nitroarenes. *IARC Monographs for the Evaluation of Carcinogenic Risk to Humans.* International Agency for Research on Cancer, Lyon.

IARC (2013). Diesel and gasoline engine exhaust and some nitroarenes. *IARC Monographs for the Evaluation of Carcinogenic Risk to Humans.* International Agency for Research on Cancer, Lyon.

Ichinose, T., Yamanushi, T., Seto, H., and Sagai, M. (1997). Oxygen radicals in lung carcinogenesis accompanying phagocytosis of diesel exhaust particles. *Int. J. Oncol.* **11**, 571–575.

Ishihara, Y., and Kagawa, J. (2003). Chronic diesel exhaust exposures of rats demonstrate concentration and time-dependent effects on pulmonary inflammation. *Inhal. Toxicol.* **15**, 473–492.

Iwai, K., Adachi, S., Takahashi, M., Moller, L., Udagawa, T., Mizuno, S., and Sugawara, I. (2000). Early oxidative DNA damages and late development of lung cancer in diesel exhaust-exposed rats. *Environ. Res.* **84**, 255–264.

Kato, A., Nagai, A., and Kagawa, J. (2000). Morphological changes in rat lung after long-term exposure to diesel emissions. *Inhal. Toxicol.* **12**, 469–490.

Khalek, I. A., Bougher, T. L., Merritt, P. M., and Zielinska, B. (2011). Regulated and unregulated emissions from highway heavy-duty diesel engines complying with US Environmental Protection Agency 2007 emissions standards. *J. Air Waste Manage.* **61**, 427–442.

Knudsen, L. E., Gaskell, M., Martin, E. A., Poole, J., Scheepers, P. T., Jensen, A., Autrup, H., and Farmer, P. B. (2005). Genotoxic damage in mine workers exposed to diesel exhaust, and the effects of glutathione transferase genotypes. *Mutat. Res.* **583**, 120–132.

Kuusimäki, L., Peltonen, Y., Mutanen, P., Peltonen, K., and Savela, K. (2004). Urinary hydroxy-metabolites of naphthalene, phenanthrene and pyrene as markers of exposure to diesel exhaust. *Int. Arch. Occup. Environ. Health* **77**, 23–30.

Lamb, C. M., Hazari, M. S., Haykal-Coates, N., Carll, A. P., Krantz, Q. T., King, C., Winsett, D. W., Cascio, W. E., Costa, D. L., and Farraj, A. K. (2012). Divergent electrocardiographic responses to whole and particle-free diesel exhaust inhalation in spontaneously hypertensive rats. *Toxicol. Sci.* **125**, 558–568.

Levesque, S., Taetzsch, T., Lull, M. E., Kodavanti, U., Stadler, K., Wagner, A., Johnson, J. A., Duke, L., Kodavanti, P., Surace, M. J., *et al.* (2011). Diesel exhaust activates and primes microglia: Air pollution, neuroinflammation, and regulation of dopaminergic neurotoxicity. *Environ. Health Perspect.* **119**, 1149–1155.

Li, N., Xia, T., and Nel, A. E. (2008). The role of oxidative stress in ambient particulate matter-induced lung diseases and its implications in the toxicity of engineered nanoparticles. *Free Rad. Biol. Med.* **44**, 1689–1699.

Liu, Z. G., Berg, D. R., Vasys, V. N., Dettmann, M. E., Zielinska, B., and Schauer, J. J. (2010). Analysis of C-1, C-2, and C-10 through C-33 particle-phase and semi-volatile organic compound emissions from heavy-duty diesel engines. *Atmos. Environ.* **44**, 1108–1115.

Lucking, A. J., Lundback, M., Barath, S. L., Mills, N. L., Sidhu, M. K., Langrish, J. P., Boon, N. A., Pourazar, J., Badimon, J. J., Gerlofs-Nijland, M. E., *et al.* (2011). Particle traps prevent adverse vascular and prothrombotic effects of diesel engine exhaust inhalation in men. *Circulation* **123**, 1721–1728.

Lundback, M., Mills, N. L., Lucking, A., Barath, S., Donaldson, K., Newby, D. E., Sandstrom, T., and Blomberg, A. (2009). Experimental exposure to diesel exhaust increases arterial stiffness in man. *Particle Fibre Toxicol* **6**, 7.

Ma, J. Y., and Ma, J. K. (2002). The dual effect of the particulate and organic components of diesel exhaust particles on the alteration of pulmonary immune/inflammatory responses and metabolic enzymes. *J. Environ. Sci. Health C* **20**, 117–147.

Matsumoto, A., Hiramatsu, K., Li, Y., Azuma, A., Kudoh, S., Takizawa, H., and Sugawara, I. (2006). Repeated exposure to low-dose diesel exhaust after allergen challenge exaggerates asthmatic responses in mice. *Clin. Immunol.* **121**, 227–235.

Mauderly, J. L., Snipes, M. B., Barr, E. B., Belinsky, S. A., Bond, J. A., Brooks, A. L., Chang, I. Y., Cheng, Y. S., Gillett, N. A., Griffith, W. C., *et al.* (1994). Pulmonary toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats. Part I: Neoplastic and nonneoplastic lung lesions. *Res. Rep. Health Eff. Inst.* **68**, 1–75.

McClellan, R. O., Hesterberg, T. W., and Wall, J. C. (2012). Evaluation of carcinogenic hazard of diesel engine exhaust needs to consider revolutionary changes in diesel technology. *Regul. Toxicol. Pharm.* **63**, 225–258.

McDonald, J. D., Barr, E. B., White, R. K., Chow, J. C., Schauer, J. J., Zielinska, B., and Grosjean, E. (2004). Generation and characterization of four dilutions of diesel engine exhaust for a suhchronic inhalation study. *Environ. Sci. Technol.* **38**, 2513–2522.

McDonald, J. D., Campen, M. J., Harrod, K. S., Seagrave, J., Seilkop, S. K., and Mauderly, J. L. (2011). Engine-operating load influences diesel exhaust composition and cardiopulmonary and immune responses. *Environ. Health Persp.* **119**, 1136–1141.

McDonald, J. D., Doyle-Eisele, M., Seagrave, J., Gigliotti, A. P., Chow, J., Zielinska, B., Mauderly, J. L., Seilkop, S. K., Miller, R. A., and Committee, H. E. I. H. R. (2015). Part 1. Assessment of carcinogenicity and biologic responses in rats after lifetime inhalation of new-technology diesel exhaust in the ACES bioassay. *Res. Rep. Health Eff. Inst.* **184**, 9–44; discussion 141–171.

Miller, M. R., Shaw, C. A., and Langrish, J. P. (2012). From particles to patients: Oxidative stress and the cardiovascular effects of air pollution. *Future Cardiol.* **8**, 577–602.

Mills, N. L., Miller, M. R., Lucking, A. J., Beveridge, J., Flint, L., Boere, A. J., Fokkens, P. H., Boon, N. A., Sandstrom, T., Blomberg, A., *et al.* (2011). Combustion-derived nanoparticulate induces the adverse vascular effects of diesel exhaust inhalation. *Eur. Heart J.* **32**, 2660–2671.

Mills, N. L., Tornqvist, H., Gonzalez, M. C., Vink, E., Robinson, S. D., Soderberg, S., Boon, N. A., Donaldson, K., Sandstrom, T., Blomberg, A., *et al.* (2007). Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *New Engl. J. Med.* **357**, 1075–1082.

Morimoto, K., Kitamura, M., Kondo, H., and Koizumi, A. (1986). Genotoxicity of diesel exhaust emissions in a battery of in-vitro short-term and in-vivo bioassays. *Dev. Toxicol. Environ. Sci.* **13**, 85–101.

Mudway, I. S., Stenfors, N., Duggan, S. T., Roxborough, H., Zielinski, H., Marklund, S. L., Blomberg, A., Frew, A. J., Sandstrom, T., and Kelly, F. J. (2004). An in vitro and in vivo investigation of the effects of diesel exhaust on human airway lining fluid antioxidants. *Arch. Biochem. Biophys.* **423**, 200–212.

Nagashima, M., Kasai, H., Yokota, J., Nagamachi, Y., Ichinose, T., and Sagai, M. (1995). Formation of an oxidative DNA damage,

8-hydroxydeoxyguanosine, in mouse lung DNA after intratracheal instillation of diesel exhaust particles and effects of high dietary fat and beta-carotene on this process. *Carcinogenesis* **16**, 1441–1445.

Nakagawa, R., Kitamori, S., Horikawa, K., Nakashima, K., and Tokiwa, H. (1983). Identification of dinitropyrenes in diesel-exhaust particles. Their probable presence as the major mutagens. *Mutat. Res.* **124**, 201–211.

Nielsen, P. S., Andreassen, A., Farmer, P. B., Ovrebø, S., and Autrup, H. (1996). Biomonitoring of diesel ex-haust-exposed workers. DNA and hemoglobin adducts and urinary 1-hydroxypyrene as markers of exposure. *Toxicol. Lett.* **86**, 27–37.

Nikula, K. J., Snipes, M. B., Barr, E. B., Griffith, W. C., Henderson, R. F., and Mauderly, J. L. (1995). Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. *Fundam. Appl. Toxicol.* **25**, 80–94.

Nordenhall, C., Pourazar, J., Ledin, M. C., Levin, J. O., Sandstrom, T., and Adelroth, E. (2001). Diesel exhaust enhances airway responsiveness in asthmatic subjects. *Eur. Respir. J.* **17**, 909–915.

Ong, T., Whong, W. Z., Xu, J., Burchell, B., Green, F. H., and Lewis, T. (1985). Genotoxicity studies of rodents exposed to coal dust and diesel emission particulates. *Environ. Res.* **37**, 399–409.

Ono, N., Oshio, S., Niwata, Y., Yoshida, S., Tsukue, N., Sugawara, I., Takano, H., and Takeda, K. (2008). Detrimental effects of prenatal exposure to filtered diesel exhaust on mouse spermatogenesis. *Arch. Toxicol.* **82**, 851–859.

Ono, N., Oshio, S., Niwata, Y., Yoshida, S., Tsukue, N., Sugawara, I., Takano, H., and Takeda, K. (2007). Prenatal exposure to diesel exhaust impairs mouse spermatogenesis. *Inhal. Toxicol.* **19**, 275–281.

Osterholm, A. M., Falt, S., Lambert, B., and Hou, S. M. (1995). Classification of mutations at the human HPRT-locus in T-lymphocytes of bus maintenance workers by multiplex-PCR and reverse transcriptase-PCR analysis. *Carcinogenesis* **16**, 1909–1912.

Pereira, M. A. (1982). Genotoxicity of diesel exhaust emissions in laboratory animals. *Dev. Toxicol. Environ. Sci.* **10**, 265–276.

Pereira, M. A., Connor, T. H., Meyne, J., and al, e. (1981). Metaphase analysis, micronucleus assay and urinary mutagenicity assay of mice exposed to diesel emissions. *Environ. Int.* **5**, 435–438.

Peretz, A., Sullivan, J. H., Leotta, D. F., Trenga, C. A., Sands, F. N., Allen, J., Carlsten, C., Wilkinson, C. W., Gill, E. A., and Kaufman, J. D. (2008). Diesel exhaust inhalation elicits acute vasoconstriction in vivo. *Environ. Health Perspect.* **116**, 937–942.

Pronk, A., Coble, J., and Stewart, P. A. (2009). Occupational exposure to diesel engine exhaust: A literature review. *J. Expo. Sci. Environ. Epidemiol.* **19**, 443–457.

Riedl, M. A., Diaz-Sanchez, D., Linn, W. S., Gong, H., Jr, Clark, K. W., Effros, R. M., Miller, J. W., Cocker, D. R., Berhane, K. T., and Committee, H. E. I. H. R. (2012). Allergic inflammation in the human lower respiratory tract affected by exposure to diesel exhaust. *Res. Rep. Health Eff. Inst.* **165**, 5–43; discussion 45–64.

Rivedal, E., Myhre, O., Sanner, T., and Eide, I. (2003). Supplemental role of the Ames mutation assay and gap junction intercellular communication in studies of possible carcinogenic compounds from diesel exhaust particles. *Arch. Toxicol.* **77**, 533–542.

Sagai, M., Saito, H., Ichinose, T., Kodama, M., and Mori, Y. (1993). Biological effects of diesel exhaust particles. I. In vitro production of superoxide and in vivo toxicity in mouse. *Free Rad. Biol. Med.* **14**, 37–47.

Salmeen, I., Durisin, A. M., Prater, T. J., Riley, T., and Schuetzle, D. (1982). Contribution of 1-nitropyrene to direct-acting Ames assay mutagenicities of diesel particulate extracts. *Mutat. Res.* **104**, 17–23.

Salvi, S., Blomberg, A., Rudell, B., Kelly, F., Sandstrom, T., Holgate, S. T., and Frew, A. (1999). Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am. J. Resp. Crit. Care Med.* **159**, 702–709.

Sato, H., Sone, H., Sagai, M., Suzuki, K. T., and Aoki, Y. (2000). Increase in mutation frequency in lung of Big Blue rat by exposure to diesel exhaust. *Carcinogenesis* **21**, 653–661.

Schoket, B., Poirier, M. C., Mayer, G., Torok, G., Kolozsi-Ringelhann, A., Bognar, G., Bigbee, W. L., and Vincze, I. (1999). Biomonitoring of human genotoxicity induced by complex occupational exposures. *Mutat. Res.* **445**, 193–203.

Silverman, D. T., Samanic, C. M., Lubin, J. H., Blair, A. E., Stewart, P. A., Vermeulen, R., Coble, J. B., Rothman, N., Schleiff, P. L., Travis, W. D., *et al.* (2012). The diesel exhaust in miners study: A nested case–control study of lung cancer and diesel exhaust. *J. Natl. Cancer Inst.* **104**, 855–868.

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

Stenfors, N., Nordenhall, C., Salvi, S. S., Mudway, I., Soderberg, M., Blomberg, A., Helleday, R., Levin, J. O., Holgate, S. T., Kelly, F. J., *et al.* (2004). Different airway inflammatory responses in asthmatic and healthy humans exposed to diesel. *Eur. Respir. J.* **23**, 82–86.

Stinn, W., Teredesai, A., Anskeit, E., Rustemeier, K., Schepers, G., Schnell, P., Haussmann, H. J., Carchman, R. A., Coggins, C. R., and Reininghaus, W. (2005). Chronic nose-only inhalation study in rats, comparing room-aged sidestream cigarette smoke and diesel engine exhaust. *Inhal. Toxicol.* **17**, 549–576.

Tanaka, M., Aoki, Y., Takano, H., Fujitani, Y., Hirano, S., Nakamura, R., Sone, Y., Kiyono, M., Ichinose, T., Itoh, T., *et al.* (2013). Effects of exposure to nanoparticle-rich or -depleted diesel exhaust on allergic pathophysiology in the murine lung. *J. Toxicol. Sci.* **38**, 35–48.

Taxell, P., and Santonen, T. (2016). *The Nordic Expert Group for criteria documentation of health risks from chemicals and the Dutch Expert Committee on Occupational Safety*. 149. Diesel Engine Exhaust. *Arbete Och Hälsa* **49**, 1–147.

Tokiwa, H., and Ohnishi, Y. (1986). Mutagenicity and carcinogenicity of nitroarenes and their sources in the environment. *Crit. Rev. Toxicol.* **17**, 23–60.

Tong, H., Rappold, A. G., Caughey, M., Hinderliter, A. L., Graff, D. W., Berntsen, J. H., Cascio, W. E., Devlin, R. B., and Samet, J. M. (2014). Cardiovascular effects caused by increasing concentrations of diesel exhaust in middle-aged healthy GSTM1 null human volunteers. *Inhal. Toxicol.* **26**, 319–326.

Tsukue, N., Kato, A., Ito, T., Sugiyama, G., and Nakajima, T. (2010). Acute effects of diesel emission from the urea selective catalytic reduction engine system on male rats. *Inhal. Toxicol.* **22**, 309–320.

Tsukue, N., Toda, N., Tsubone, H., Sagai, M., Jin, W. Z., Watanabe, G., Taya, K., Birumachi, J., and Suzuki, A. K. (2001). Diesel exhaust (DE) affects the regulation of testicular function in male Fischer 344 rats. *J. Toxicol. Environ. Health A* **63**, 115–126.

USEPA. (2002). *Health Assessment Document for Diesel Engine Exhaust*. U.S. Environmental Protection Agency, Washington, DC.

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

Villarini, M., Moretti, M., Fatigoni, C., Agea, E., Dominici, L., Mattioli, A., Volpi, R., and Pasquini, R. (2008). Evaluation of primary DNA damage, cytogenetic biomarkers and genetic polymorphisms for CYP1A1 and GSTM1 in road tunnel construction workers. *J. Toxicol. Environ. Health A* **71**, 1430–1439.

Westerholm, R. N., Almen, J., Li, H., Rannug, J. U., Egebaeck, K. E., and Graegg, K. (1991). Chemical and biological characterization of particulate-, semivolatile-, and gas-phase-associated compounds in diluted heavy-duty diesel exhausts: A comparison of three different semivolatile-phase samplers. *Environ. Sci. Technol.* **25**, 332–338.

WHO. (1997). *Nitrogen Oxides. Environmental Health Criteria*. World Health Organization, Geneva.

Wierzbicka, A., Nilsson, P. T., Rissler, J., Sallsten, G., Xu, Y. Y., Pagels, J. H., Albin, M., Osterberg, K., Strandberg, B., Eriksson, A., Bohgard, M., *et al.* (2014). Detailed diesel exhaust characteristics including particle surface area and lung deposited dose for better understanding of health effects in human chamber exposure studies. *Atmos. Environ.* **86**, 212–219.

Win-Shwe, T. T., Yamamoto, S., Fujitani, Y., Hirano, S., and Fujimaki, H. (2012). Nanoparticle-rich diesel exhaust affects hippocampal-dependent spatial learning and NMDA receptor subunit expression in female mice. *Nanotoxicology* **6**, 543–553.

Win-Shwe, T. T., Yamamoto, S., Fujitani, Y., Hirano, S., and Fujimaki, H. (2008). Spatial learning and memory function-related gene expression in the hippocampus of mouse exposed to nanoparticle-rich diesel exhaust. *Neurotoxicology* **29**, 940–947.

Yokota, S., Moriya, N., Iwata, M., Umezawa, M., Oshio, S., and Takeda, K. (2013). Exposure to diesel exhaust during fetal period affects behavior and neurotransmitters in male offspring mice. *J. Toxicol. Sci.* **38**, 13–23.

Yoshida, S., Sagai, M., Oshio, S., Umeda, T., Ihara, T., Sugamata, M., Sugawara, I., and Takeda, K. (1999). Exposure to diesel exhaust affects the male reproductive system of mice. *Int. J. Androl.* **22**, 307–315.