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REVIEW PAPER

Critical Review of Diesel Exhaust Exposure Health Impact Research Relevant to Occupational Settings: Are We Controlling the Wrong Pollutants?

Katherine R. Landwehr[1,2] · Alexander N. Larcombe[1,2] · Alison Reid[1] · Benjamin J. Mullins[1]

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Abstract
Diesel exhaust emissions and exposure of workers in occupational settings are topics which have attracted increased attention after IARC classification as a group 1 carcinogen (IARC. Agents classified by the IARC monographs, Vols. 1–120. International Agency for the Research on Cancer. http://monographs.iarc.fr/ENG/Classification/. Accessed 21 Feb 2018; 2018). There is ongoing debate over appropriate exposure limits for occupationally exposed workers. This review consolidates recent research findings relevant to setting appropriate exposure limits, with a specific focus on newer engine and after-treatment technologies. Appropriate online databases were searched for studies published since 2005 focussing on the health effects of whole diesel exhaust exposure. Engines that used exhaust after-treatment devices including both a diesel oxidation catalyst and a diesel particulate filter were classified as new technology engines. All other studies were classified as using older technology engines. Exposure to diesel exhaust from both engine classifications resulted in negative health impacts on the lungs, heart and brain. Study participants with asthma, allergy or respiratory disease were more at risk of negative effects caused by diesel exhaust exposure than healthy subjects. Based on the published literature, an occupational limit of an average diesel exhaust concentration below 50 μg/m^3 of diesel exhaust particles, 35 μg/m^3 of elemental carbon, is appropriate to limit health effects. To meet this limit, many diesel engines will need to be equipped with after-treatment technology such as a DPF. However, the use of a DPF had little to no impact on measured health effects despite the removal of over 90% by weight of particles. This negates the feasibility of using particle mass-based limits.

Keywords Diesel Exhaust Exposure · Occupational Exhaust Exposure · Occupational Exposure Limit · Occupational Diesel Exhaust Limit

Diesel Exhaust

Diesel exhaust was classified as a class 2a, probable human carcinogen by the International Agency for Research on Cancer (IARC) in 1989. This classification changed to class 1, definitely carcinogenic to humans in 2012 (IARC 2018) based primarily on a series of studies conducted on 12,315 occupationally exposed hardrock miners. The risk was greatest in surface workers with a standard mortality ratio (SMR) of 1.33 (1.06–1.66, 95% C.I.) compared with underground workers 1.21 (1.01–1.45, 95% C.I.), despite the underground workers having an average respirable elemental carbon (EC) exhaust exposure level that was over 75 times higher than the surface workers. This may be attributed to background exposures unrelated to DE in the study population or the effect of DE ageing and being exposed to sunlight, ozone and other environmental factors which can cause DE components to become more toxic (Attfield et al. 2012; Silverman et al. 2012).

Diesel exhaust can be separated into two main components: the gaseous phase and the particulate matter (PM) phase. Gaseous components include carbon monoxide (CO), carbon dioxide (CO_2), nitrogen oxides (NO_x) and sulphur dioxide (SO_2) as well as additional gas phase chemical species such as polycyclic aromatic hydrocarbons (PAH) and volatile organic

✉ Katherine R. Landwehr
katherine.landwehr@telethonkids.org.au

[1] School of Public Health, Curtin University, PO Box U1987, Perth, WA 6845, Australia

[2] Respiratory Environmental Health, Telethon Kids Institute, Perth Children's Hospital, Nedlands, Perth, WA 6009, Australia

compounds (VOC). The PM is composed of mostly solid EC particles with potentially toxic chemicals such PAH, VOC, aldehydes, ketones and heavy metals ad/absorbed to the particles (Carrara and Niessner 2011; Fontaras et al. 2009; Hu et al. 2013; Prokopowicz et al. 2015; Riley et al. 2018). Diesel exhaust can contain hundreds of different chemical species and concentrations can change significantly depending on engine type, speed, load, whether accelerating or decelerating, starting temperature and the usage of exhaust after-treatment devices (Bünger et al. 2000; Fontaras et al. 2009; Hemmingsen et al. 2011; Hesterberg et al. 2011; Karavalakis et al. 2009; Khalek et al. 2011; Kisin et al. 2013).

Of most concern are the ultrafine particles found within DE. These particles, at less than 100 nm in size, comprise the majority of DE PM with particles smaller than 30 nm comprising over 90% of the total number of particles but only accounting for 10% of the total PM mass (Kittelson et al. 2002; Ris 2007). Ultrafine particles are capable of penetrating deeper into the lungs than larger sized particles, dispersing over a greater percentage of lung volume and thus causing a greater respiratory irritant effect (Oberdörster et al. 1995; Seaton et al. 1995). Smaller particles have a greater surface area-to-volume ratio, meaning that a greater amount of potentially toxic substances can adhere to the surface for a given mass of PM (Mullins et al. 2016; Yoza et al. 2002) and thus a greater amount of toxic chemicals are deposited in the lungs. Exposure to ultrafine particles is associated with pulmonary inflammation (Oberdörster et al. 1995) and exacerbation of existing lung diseases including asthma (Evans et al. 2014; Seaton et al. 1995). Ultrafine particles are also capable of penetrating into the cardiovascular system and cause a range of adverse health effects including increased blood pressure and heart failure (Brook et al. 2010).

Alone, each individual component of the exhaust can cause its own unique health effects and combined they can interact to cause more complicated health impacts such as cancer as well as impacting the cardiovascular, respiratory and neurological systems (Benbrahim-Tallaa et al. 2012; Cosselman et al. 2012; Heidari Nejad et al. 2015; Larcombe et al. 2014; Levesque et al. 2011a; Mills et al. 2007; Zhu et al. 2012). This makes studying the effects of whole exhaust preferable to those of isolated components, such as PM alone, where the effects of the gas components and their interaction with PM is lost (Abe et al. 2000; Larcombe et al. 2015).

Changes in Engine Technology, Exhaust After-Treatment Devices and Emission Limits

Using diesel particulate filters (DPF), diesel oxidation catalysts (DOC) and other exhaust after-treatment devices, the components of DE change dramatically. A DPF is capable of removing approximately 90% of PM by mass. Elemental carbon is preferentially removed and ratios of EC to organic carbon reduce from ~3 to 0.5 (Khalek et al. 2011). In exhaust without a DPF, EC makes up approximately 75% of PM by weight (US EPA 2002), which reduces to approximately 13% after the use of a DPF. In the ultrafine particle range, larger sized particles closer to 100 nm in size are removed from the exhaust more successfully than smaller sizes (Khalek et al. 2011).

The EURO, US EPA and the US TIER classification systems have been developed as emission standards for light-heavy vehicles on road, heavy duty vehicles on road and off road engine emissions, respectively. Most engines classified as EURO IV, US EPA 2007 or US TIER 4 and above require exhaust after-treatment devices for compliance and engines classified as EURO IV and above generally require the latest high-pressure common-rail electronic fuel injection systems (Dallmann and Menon 2016). The aim of this review is to consolidate recent DE exposure and health effects research findings relevant to setting appropriate DE exposure limits, with a specific focus on newer engine and after-treatment technologies.

Methods

PubMed was searched using "Diesel Exhaust" combined with the individual search term "Exposure Health Effect", limiting the search to results published after 2005 and finding over 600 studies that matched the search criteria. In addition, the databases Embase and Cinahl Plus were searched using the term "Diesel Exhaust Exposure Health Effect", limiting the search to results not included as part of the PubMed/Medline database and studies published after 2005. Over 200 studies matched the search criteria. Only articles from the search which matched the review criteria, as well as relevant cited references therein, were reviewed. Studies were excluded if they were not in English, if the results were based on data obtained before 2005, if the diesel fuel used was not classified as ultra-low-sulphur diesel (<15 ppm sulphur), or if it exceeded 10% biodiesel concentration, if whole exhaust was not used and finally if the concentration of the exhaust used or the health outcomes measured were not relevant to occupational exposure settings.

The cut-off date of 2005 was selected based on diesel fuel legislation to limit sulphur levels in commercial diesel fuel. The legislation was introduced in multiple countries in the mid-2000s with several years taken to complete the change over (Kavanagh 2014). If studies did not specify the amount of sulphur within the diesel fuel used, assumptions were made based on the country the study was performed in and the date that the legislation for ultra-low-sulphur diesel

was introduced. If the date of publication fell outside of that range, the study was excluded (Fig. 1).

Relevant studies were separated into occupational exposure studies, acute human exposure studies, in vivo exposure studies and in vitro exposure studies. Acute human exposure, in vivo and in vitro studies were further separated into the use of new or older technology engines. Studies that used exhaust from an engine either classified as EURO IV, US EPA 2007 or TIER 4 and above, or as being paired with a DPF and DOC, were classified as using new technology engines. Studies that did not specify engine type, used exhaust from an engine without both after-treatment devices or used an engine at a lower EURO or TIER classification were defined as using older technology.

Occupational Exposure Studies

A common method of completing occupational exposure studies is to focus on population data in order to collect potential health consequences of DE exposure. As a consequence, the majority of DE exposure data are obtained before 2000, for example (Attfield et al. 2012; Kachuri et al. 2016; Olsson et al. 2011; Silverman et al. 2012; Vermeulen et al. 2014), when sulphur levels in fuel were high (>500 ppm and in some cases >5000 ppm) (Kavanagh 2014) and diesel engines were not equipped with exhaust after-treatment devices. In order to measure the consequences of a lifetime of occupational exposure to a substance, a lifetime has to have passed, making such studies difficult when the substance being measured (i.e. new technology diesel engine exhaust) is still newly introduced into the workplace. Thus, few studies have looked at new technology exhaust and fewer still have looked at the health consequences of exposure. Since the occupational studies reviewed did not

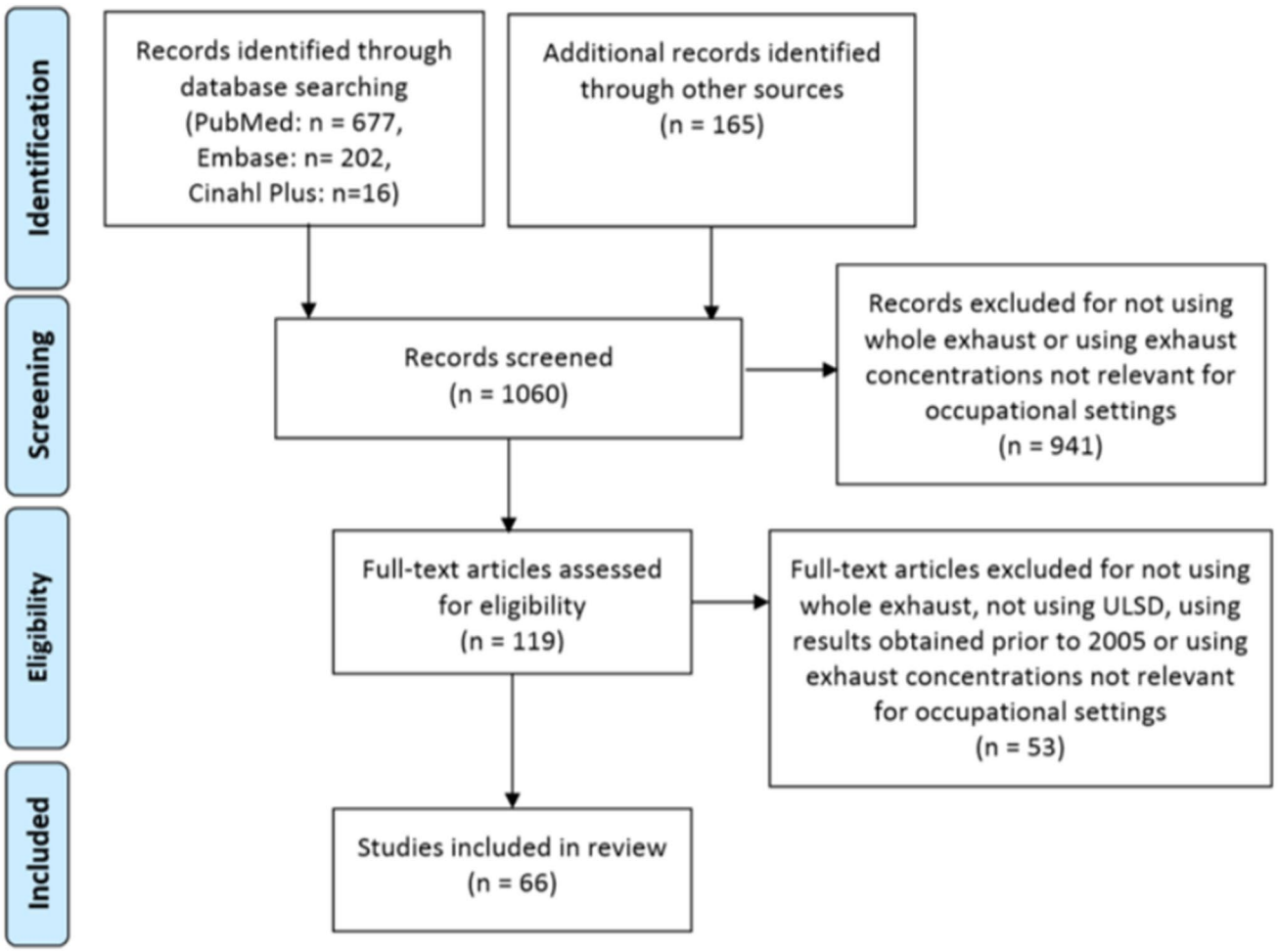

Fig. 1 An overview of the methodology used to select appropriate articles for review

specify the type of engine technology used, all are classified as old technology studies.

That said, studies focussing on populations that have been more recently exposed to DE at occupational concentrations have been published (Table 1), including a series of studies on a cohort of diesel engine testers in China (Bassig et al. 2017; Dai et al. 2018; Niu et al. 2018; Wang et al. 2017). These studies found that the greater the concentrations of DE exposure and the longer the time period the workers had been exposed for, the more the immune response was dysregulated (Dai et al. 2018; Wang et al. 2017), with the highest exposure levels (greater than 397 μg/m^3) resulting in significantly lower inflammatory cytokine levels in blood serum (Dai et al. 2018). This was theorized to be a mechanism for increased lung cancer risk as the immune system has an important role in eliminating cancerous cells. Exposure to ~282 μg/m^3 resulted in decreased lung function, compared to control subjects with an exposure level of ~92 μg/m^3 (Wang et al. 2017). At DE exposure concentrations of ~268 μg/m^3, increased DNA damage was found in peripheral blood lymphocytes, as well as DNA hypomethylation changes associated with DNA damage in blood samples of exposed subjects, compared to control subjects exposed to DE concentrations of ~92 μg/m^3 (Zhang et al. 2015, 2016b). Occupational DE exposures that resulted in above 1.08 μg/g urinary creatinine, a marker of PAH exposure and corresponding to an exposure of ~170 μg/m^3 of fine PM (~110 μg/m^3 total carbon), were associated with higher levels of cancer biomarkers (Niu et al. 2018). An exposure level of approximately 100 μg/m^3 found immune alterations similar to published lung cancer risk studies, suggesting a significantly higher risk of lung cancer (Bassig et al. 2017).

Studies outside of the diesel engine tester cohort found that mechanics occupationally exposed to DE, at an estimated level of 250 μg/m^3, exhibited cytotoxic and genotoxic damage to buccal epithelial cells, and peripheral blood lymphocytes. In addition, damage to DNA in both cell types was correlated with years of service, suggesting that longer periods of exposure to DE resulted in a greater amount of DNA damage (León-Mejía et al. 2019), which has implications for lung cancer risk (Bonassi et al. 2011; León-Mejía et al. 2019). A lifetime exposure (approximately 45 years) to 14 μg/m^3 of EC in Western Australian miners was estimated to result in an increase of 5.5 (2.7–9.2, 95% confidence interval) lung cancer deaths per 1000 male workers. An exposure of 44 μg/m^3 of EC was estimated to result in an increase of 38 (19–97, 95% confidence interval) lung cancer deaths per 1000 male workers (Peters et al. 2017). Exposure was measured between 2003 and 2011 when new technology engines were still being introduced, such that the total PM exposure levels are estimated to be 19 μg/m^3 and 59 μg/m^3, respectively. Norwegian tunnel finishing workers occupationally exposed to DE at approximately 37.8 μg/m^3 of EC, (~50 μg/m^3 PM assuming that the majority of exposure was from old technology engines) found that in comparison to non-exposed control subjects, the tunnel workers had more DNA damage in their peripheral blood mononuclear cells, altered blood plasma profiles and dysregulated expression of several microRNAs, including some related to carcinogenesis, cell death and oxidative stress (Rynning et al. 2019).

Occupational DE exposure studies reported effects on lung function and biomarkers that correlated with increased cancer risk (Bassig et al. 2017; Dai et al. 2018; León-Mejía et al. 2019; Niu et al. 2018; Rynning et al. 2019; Wang et al. 2017). All studies reported increased risks of lung cancer in workers occupationally exposed to DE. Occupational exposures below 100 μg/m^3 of PM increased DNA damage, immune alterations in a pattern related to increased lung cancer incidence and an estimated risk of 38 lung cancers per 1000 workers exposed to approximately 44 μg/m^3 EC (approximately 59 μg/m^3 PM).

Acute Human Exposure Studies

We found no studies that examined the effects of new engine technology exhaust exposure on humans and only one study that focussed on the health effects of acute exposure to DE with and without a DPF on humans. Thus, all studies that involve acute exposure of humans to high levels of DE have used old technology diesel engines. All but two studies used exposure chambers and participants were exposed to either diluted whole DE at a variety of concentrations and/or air as a control. The measured end points focussed primarily on the cardiovascular system with fewer studies focusing on the respiratory system. No study exposed participants to DE for more than three hours. Further information on the exposure methodology can be found in Table 2.

Studies using DE exposure concentrations between 350 and 300 μg/m3 found minor and major cardiovascular effects with increased arterial stiffness (Lundbäck et al. 2009), increased endothelial dysfunction in patients at risk for heart failure (Vieira et al. 2016), reduced vasodilation (Lucking et al. 2011; Mills et al. 2011), increased thrombus formation (Lucking et al. 2011) and increased blood pressure after two hours of exposure (Mills et al. 2011; Tong et al. 2014). In addition, altered blood plasma profiles were found in healthy individuals and altered blood plasma profiles and altered microRNA expression in peripheral blood were found in individuals with an allergy or asthma (Giles et al. 2018b; Yamamoto et al. 2013; Zhang et al. 2016a). DNA hypomethylation was found in genes associated with oxidative stress and inflammation in asthmatics (Jiang et al. 2014). Respiratory effects have also been reported, with altered microRNA and transcription profiles and DNA hypomethylation associated with increased oxidative stress in epithelial

Table 1 Key data from selected occupational human exposure studies using old technology DE

Average Concentration of Diesel Exhaust PM (µg/m3, mean (±SD))	Source	Cohort Demographic	Health Outcomes
19*	Peters et al. (2017)	Personal EC exposure for 8614 Australian Miners collected between 2003 and 2015	Increased lung cancer risk: estimated 5.5 (2.7–9.2, 95% C.I.) extra lung cancer deaths per 1000 workers
50*	Rynning et al. (2019)	69 Norwegian tunnel finishing workers and 69 unexposed control subjects working at similar construction sites	Increased DNA damage in peripheral blood mononuclear cells in never smoking, former smoking and daily smoking subjects ((~mean; 5th–95th percentile DNA adducts per 10^8 nucleotides) control vs exposed for never smoking, former smoking and daily smoking subjects: 0.87; 0.64–1.12 vs 1.03, 0.74–1.33, 0.91; 0.69–1.22 vs 1.24; 0.79–1.90, 1.10; 0.90–1.26 vs 1.48; 0.97–2.01, respectively). MicroRNA dysregulation, including several related to carcinogenesis, cell death and oxidative stress
59*	Peters et al. (2017)	Personal EC exposure for 8614 Australian Miners collected between 2003 and 2015	Increased lung cancer risk: estimated 38 (19–97, 95% C.I.) extra lung cancer deaths per 1000 workers
100	Bassig et al. (2017)	54 male workers employed at a diesel engine testing facility and 55 unexposed male control workers	Levels of nine inflammatory markers altered in directions associated with lung cancer risk. The largest differences between control and exposed subjects were found in CRP (42.7% decrease), IL-21 (23.5% decrease) and CCL15 (21.2% increase) (mean ± SD (pg/ml) in control vs exposed: $1.6\times107 \pm 2.3\times107$ vs $9.2\times106 \pm 1.4\times107$, 3.4 ± 8.6 vs 2.6 ± 4.9 and 2260.4 ± 997.2 vs 2740.5 ± 1098.4, respectively
~170	Niu et al. (2018)	137 male exposed diesel engine tester and 127 male non-exposed workers	Exceeding 1.08 µg/g urinary creatinine, approximately 110 µg/m3 total carbon exposure, was associated with increased cancer biomarkers such as micronucleus, and thus increased risk of cancer
250	León-Mejía et al. (2019)	120 diesel exhaust exposed Columbian mechanics and 100 unexposed control subjects	Cytotoxic and genotoxic damage to buccal epithelial cells and peripheral blood lymphocytes ((mean ± SD) frequency of micronucleation in buccal epithelial cells control vs exposed: 6.13 ± 2.49 vs 16.89 ± 10.16 ($p < 0.001$). Comet assay damage index, % tail DNA and frequency of micronucleation in blood lymphocytes, control vs exposed: 107.05 ± 27.88 vs 131.22 ± 48.15 ($p < 0.05$), 23.39 ± 9.18 vs 30.91 ± 17.52 ($p < 0.05$) and 4.02 ± 2.54 vs 10.36 ± 6.56 ($p < 0.001$)). Micronucleation of lymphocytes correlated with years of service ($r = 0.370$, $p < 0.0001$)
268	Zhang et al. (2015)	117 male exposed diesel engine tester and 112 male non-exposed control workers	Increased DNA damage in peripheral blood lymphocytes, in comparison to exposures at 92 µg/m3. Exposed workers exhibited a 2-, 7.8-, and 4.3-fold increase in the means of the micronucleus, nucleoplasmic bridge and nuclear bud frequencies (mean ± SD of control vs exposed subjects: $3.54\% \pm 2.64\%$ vs $7.04\% \pm 3.32$, $0.22\% \pm 0.46\%$ vs $1.71\% \pm 1.28\%$, $1.18\% \pm 1.37\%$ vs $5.11\% \pm 3.63\%$, respectively)

Table 1 (continued)

Average Concentration of Diesel Exhaust PM (µg/m3, mean (±SD))	Source	Cohort Demographic	Health Outcomes
268	Zhang et al. (2016b)	117 male exposed diesel engine tester and 112 male non-exposed control workers	DNA hypomethylation of three DNA damage response genes (p16, RASSFIA and MGMT) and slight immune dysregulation in comparison to exposures at 92 µg/m3. Methylation in p16, RASSF1A, and MGMT decreased by 0.36% (0.11–0.60%, 95% C.I), 0.46% (0.14–0.79%, 95% C.I.) and 0.55% (0.15–0.95%, 95% C.I.), respectively, and monocyte levels were lower in exposed workers (5.01% ± 1.72% vs 4.40% ± 1.12%, p = 0.014)
282	Wang et al. (2017)	117 male exposed diesel engine tester and 112 male non-exposed control workers	Lower lung function, decreased serum markers of local inflammation and increased serum markers of systemic inflammation in comparison to exposures at 92 µg/m3. The longer the exposed workers had worked at the facility, the greater the immune dysregulation displayed. Measures of FEV1/FVC decreased from 88.5% (80.5–98.1%, 90% C.I.) to86.0%(76.5–94.0%, 90% C.I.). Local inflammation was measured using serum CC16 (17.1 ng/ml (9.3–29.1 ng/ml, 90% C.I.) vs 13.9 ng/ml (7.5–25.6 ng/ml, 90% C.I.) in healthy vs exposed subjects); systemic inflammation was measured using serum CRP levels (0.47 ng/ml (0.06–6.36 ng/ml, 90% C.I.) vs 0.91 ng/ml (0.30–4.90 ng/ml, 90% C.I.)
>397	Dai et al. (2018)	41 male exposed diesel engine testers and 46 male unexposed controls	Reduced inflammatory cytokine response in blood serum. Cytokines IL-8 and Mip-1β had significantly decreased release in the highest exposed subjects (median (pg/ml) (10-90th percentile) in healthy vs exposed subjects = 11.9 (8.5–18.1) vs 9.4 (8.4–11.9) and 71.1 (31.4–130.8) vs 30.8 (8.9–59.4), respectively). Cytokine MCP-1 also displayed a significant inverse relationship with exposure levels

Studies use average PM/EC readings to assess levels in the work place and thus assume that workers are exposed to the measured level of diesel exhaust for the entirety of their shifts. All EC measurements are assumed to be from old technology engines (~75% of the total PM measurement)

SEM standard error of the mean, *SD* standard deviation, *C.I.* confidence interval

~ Data obtained from graphical forms and thus are an approximation only

*Exposure levels measured in EC, adjusted to PM

Table 2 Key experimental data from selected acute human exposure studies using old technology DE

Concentration of Diesel Exhaust (µg/m3)	Source	8 Hour TWA (µg/m^3)	Exposure Time (hours)	Times Exposed to Diesel Exhaust	Cohort Demographic	Exposure Method	Engine Classification	Health Impacts in Acute Exposures
7.2	Lucking et al. (2011)	0.9	1	2	19 non-smoking healthy males (mean age, 25 ± 3 years)	Exposure chamber	NS*	Exhaust paired with a DPF had no impact on vasoconstriction and mild increased thrombotic effects in comparison to more severe effects at 320 µg/m^3 unfiltered exhaust (increase of approximately 4% in stenosed coronary artery simulation, not significant compared to either air or unfiltered exhaust. Not significantly different to air in patent coronary arteries but significantly decreased in comparison to the unfiltered exhaust)
<75	Zhang et al. (2009)	<18.75	2	1	60 non-smoking asthmatics (18–55 years old)	Controlled roadside exposure	Mix	Decreased lung function, increased airway acidification and increased respiratory inflammation in asthmatics; more severe asthmatics displayed greater symptoms ((mean ± SE); FEV1 and FVC decreased by 3.23% ± 1.04% and 3.06% ± 0.29%, respectively, two hours after DE exposure ($p = 0.004$); exhaled breath condensate pH decreased by 1.99% ± 0.05 three hours after exposure ($p = 0.002$); 22 h after exposure measurements of sputum myeloperoxidase increased by 521% ± 12.58% ($p = 0.014$))

Table 2 (continued)

Concentration of Diesel Exhaust (µg/m3)	Source	8 Hour TWA (µg/m^3)	Exposure Time (hours)	Times Exposed to Diesel Exhaust	Cohort Demographic	Exposure Method	Engine Classification	Health Impacts in Acute Exposures
100	Pawlak et al. (2016)	25	2	1	22 allergic rhinitics (11 exposed to air, 27.5 ± 8.7 years, 11 exposed to exhaust, 25.6 ± 4.7 years)	Exposure chamber	NS	Increased inflammation (eosinophil cationic protein levels (mean ± SD) = 92.78 ± 111.3 and 112.1 ± 97.54 for air and DE exposure, respectively ($p = 0.04$)) and prolonged viral-induced eosinophil activation effects in subjects with allergic rhinitis
100	Behndig et al. (2015)	25	2	2	32 asthmatics, 13 rhinitics and 21 healthy controls (18–41 years old)	Exposure chamber	NS[a]	No evidence of epithelial cell damage following exposure
100	Tong et al. (2014)	25	2	3	6 healthy glutathione-S-transferase-Mu 1 null adults (50–71 years old)	Exposure chamber	NS	No cardiovascular effects, increased inflammatory effects (18 h pose exposure fold change (95% C.I.) for venous blood monocyte counts of 1.22 (1.00, 1.44) ($p < 0.05$))
100	Peretz et al. (2008a)	25	2	2	16 healthy adults (18–49 years old)	Exposure chamber	NS[b]	No consistent cardiovascular effects
100	Peretz et al. (2008b)	25	2	2	10 healthy adults and 17 adults with metabolic syndrome (18–49 years old)	Exposure chamber	NS[b]	Half the amount of vasoconstriction (0.05 mm decrease in brachial artery diameter) in comparison to 200 µg/m3 exposures, suggesting a linear dose–response. Not significantly different to air
100	Carlsten et al. (2008)	25	2	2	16 adults with metabolic syndrome (18–49 years old)	Exposure chamber	NS[b]	No cardiovascular effects in metabolic syndrome patients

Table 2 (continued)

Concentration of Diesel Exhaust (µg/m3)	Source	8 Hour TWA (µg/m^3)	Exposure Time (hours)	Times Exposed to Diesel Exhaust	Cohort Demographic	Exposure Method	Engine Classification	Health Impacts in Acute Exposures
100	Behndig et al. (2011)	25	2	2	32 non-smoking asthmatics and 23 non-smoking healthy controls (18–45 years old)	Exposure chamber	NS[a]	Increased airway inflammation in healthy subjects but not asthmatics (submucosal neutrophil counts (~median; IQR, cells/mm^2) and bronchial wash IL-6 release (~median; IQR, pg/ml) in healthy subjects, control vs exposed: 57.3; 25.2–75.6 vs 71.1; 48.1–153.5 ($p < 0.01$), 3.1; 1.6–4.9 vs 4.9; 2.7–7.1 ($p < 0.05$))
200	Peretz et al. (2007)	50	2	3	5 non-smoking healthy adults (20–31 years old)	Exposure chamber	NS[b]	Altered genetic profile in peripheral blood mononuclear cells (2.4% or 1240 out of 54,675 probe sets significantly changed in response to DE exposure)
200	Cosselman et al. (2012)	50	2	1	45 healthy non-smokers (18–49 years old)	Exposure chamber	NS[b]	Increased blood pressure (an increase of 3.8 mmHg (95% CI: −0.4, 8.0) and 5.1 mmHg [95% CI: 0.7, 9.5] for 30 min and 60 min of exposure, respectively), no impact on heart rate
200	Allen et al. (2009)	50	2	1	10 adults with metabolic syndrome (18–49 years old)	Exposure chamber	NS[b]	No effect on patients with metabolic syndrome
200	Peretz et al. (2008a)	50	2	2	16 healthy adults (18–49 years old)	Exposure chamber	NS[b]	No consistent cardiovascular effects
200	Tong et al. 2014	50	2	3	6 healthy glutathione-S-transferase-Mu 1 null adults (50–71 years old)	Exposure chamber	NS	Increased inflammation in venous blood samples (18 h post-exposure fold change (95% C.I.) of 1.07 (0.96, 1.19) ($p < 0.05$) and 1.02 (0.97, 1.07) ($p < 0.1$) for neutrophil and platelet count, respectively), no cardiovascular effects

Table 2 (continued)

Concentration of Diesel Exhaust (µg/m3)	Source	8 Hour TWA (µg/m^3)	Exposure Time (hours)	Times Exposed to Diesel Exhaust	Cohort Demographic	Exposure Method	Engine Classification	Health Impacts in Acute Exposures
200	Peretz et al. (2008b)	50	2	2	10 healthy adults and 17 adults with metabolic syndrome (18–49 years old)	Exposure chamber	NS[b]	Increased vasoconstriction (brachial artery diameter decrease of 0.11 mm (95% C.I., 0.02–0.18))
250	Barath et al. (2010)	31.25	1	1	18 non-smoking healthy males (21–30 years old)	Exposure chamber	NS	Decreased chemically induced vasodilation (e.g. (~mean ± SEM, ml/100 ml tissue/min) forearm blood flow vasodilation after intra-brachial infusion of 1000 pmol/min bradykinin control vs exposed: 20.6 ± 1.7 vs 18.2 ± 1.7), no effect on heart rate variability, inflammation or blood pressure
280	Wierzbicka et al. (2014)	105	3	2	Healthy non-smoking adults (40–66 years old)	Exposure chamber	NS	Irritant effects—chest, throat and nose symptoms (clinically diagnosed and reported by participants using post-exposure questionnaires). No reported symptoms at 15 min of exposure. Symptoms reported after 75 min and symptoms worsened after 135 min of exposure
300	Giles et al. (2018a)	18.75	0.5	3	18 non-smoking recreationally active males (24.5 ± 6.2 years)	Exposure chamber	TIER-3c	Irritant effects—chest, throat and nose symptoms (reported by participants using post-exposure questionnaires), no changes in blood pressure

Table 2 (continued)

Concentration of Diesel Exhaust (µg/m3)	Source	8 Hour TWA (µg/m^3)	Exposure Time (hours)	Times Exposed to Diesel Exhaust	Cohort Demographic	Exposure Method	Engine Classification	Health Impacts in Acute Exposures
300	Giles et al. (2018b)	18.75	0.5	3	18 non-smoking recreationally active males (24.5 ± 6.2 years)	Exposure chamber	TIER-3c	Altered blood plasma profiles (two hours post exposure, endothelin-1 significantly decreased in comparison to air (mean ± SD (pg/ml) = 1.48 ± 0.28 and 1.36 ± 0.37 for air and DE exposures, respectively ($p = 0.037$). High-intensity exercise during exposure increased plasma NO_x levels in the DE-exposed group in comparison to controls: (~mean ± SD (µmol/L) = 19.7 ± 7.7 vs 13.8 ± 5.9, respectively. No changes in blood pressure or markers of inflammation
300	Hussain et al. (2012)	37.5	1	1	16 non-smoking asthmatics (20–42 years old)	Exposure chamber	NS	Decreased lung function, increased airway hyperactivity and obstruction in individuals with asthma (FEV1% decreased by 3.3% 24 h after exposure ($p = 0.043$), 20% reduction in forced expiratory volume in one second (PC20) decreased by 4.8 mg/ml (C.I. 95% 1.23–8.35, $p = 0.012$))
300	Rider et al. (2016)	75	2	2	15 non-smoking healthy volunteers with atopy to house dust mite, birch or Pacific grass (19–49 years old)	NS	NS	Altered microRNA and transcription profiles (expression levels of six miRNA and ten mRNA were significantly altered after exposure to DE alone)
300	Clifford et al. (2017)	75	2	1	17 non-smoking healthy adults (20–46 years old)	Exposure chamber	TIER-3c	DNA hypomethylation in airway epithelial cells. Exposure to DE or allergen primes response to second exposure

Table 2 (continued)

Concentration of Diesel Exhaust (µg/m3)	Source	8 Hour TWA (µg/m^3)	Exposure Time (hours)	Times Exposed to Diesel Exhaust	Cohort Demographic	Exposure Method	Engine Classification	Health Impacts in Acute Exposures
300	Zhang et al. (2016a)	75	2	1	17 non-smoking atopic adults (17–49 years old)	Exposure chamber	TIER-3c	Altered genetic and plasma profile, decreased lung function and increased airway hyperactivity in subjects with allergies (coexposure to DE and allergen resulted in 10.23 ± 42.0 mg/ml reduction in PC20 ($p = 0.15$) and a 5.2% mean reduction in FEV1 after DE exposure in comparison to control)
300	Jiang et al. (2014)	75	2	1	16 non-smoking asthmatics (19–35 years old)	Exposure chamber	TIER-3c	In asthmatics, changes to DNA methylation occurred at 2827 CpG sites after exposure to diesel exhaust but not filtered air. The majority of changes were hypomethylation. Methylation changes occurred in genes associated with oxidative stress and inflammation in asthmatics
300	Tong et al. (2014)	75	2	3	6 healthy glutathione-S-transferase-Mu 1 null adults (50–71 years old)	Exposure chamber	NS	Diastolic blood pressure increased by 5 mmHg ((mean ± SEM) before and after DE exposure = 78.3 ± 3.7 and 83.3 ± 4.0, respectively)
300	Cliff et al. (2016)	75	2	1	27 non-smoking healthy adults (19–49 years old)	Exposure chamber	TIER-3c	No effect on blood Central Nervous System biomarkers
300	Curran et al. (2018)	75	2	1	28 non-smoking healthy adults (19–49 years old)	Exposure chamber	TIER-3c	No effect on balance after exposure
301	Yamamoto et al. (2013)	75	2	2	13 non-smoking asthmatics (19–35 years old)	Exposure chamber	TIER-3c	In asthmatics, the expression levels of 81 microRNA's in blood were found to change after DE exposure. Changes associated with increased oxidative stress

Table 2 (continued)

Concentration of Diesel Exhaust (µg/m3)	Source	8 Hour TWA (µg/m^3)	Exposure Time (hours)	Times Exposed to Diesel Exhaust	Cohort Demographic	Exposure Method	Engine Classification	Health Impacts in Acute Exposures
320	Lucking et al. (2011)	40	1	2	19 healthy males (mean age, 25 ± 3 years)	Exposure chamber	NS	Reduced vasodilation and increased thrombus formation (forearm blood flow vasodilation (~mean ± SEM, ml/100 ml tissue/ min) decreased after intra-brachial infusion of 1000 pmol/min bradykinin control vs exposed: 19.0 ± 1.5 vs 20.5 ± 2.1. Thrombus formation increased by 21.8% ($p < 0.001$) and 14.8% ($p < 0.05$) in simulations of patent and stenosed coronary arteries, respectively, after exposure to DE). No changes in blood pressure, heart rate, markers of inflammation and platelet activation
325	Vieira et al. (2016)	14	0.35	2	26 adults at risk of heart failure (51 ± 9 years) and 15 healthy controls (45 ± 10 years)	NS	NS	Increased endothelial dysfunction in patients at risk for heart failure (decrease in the reactive hyperemia index from 2.17 (IQR: 1.8 to 2.5) to 1.72 (IQR: 1.5 to 2.2; p = 0.002) after exposure to DE. Values under 2 associated with increased endothelial dysfunction. Increased B-type natriuretic peptide in peripheral blood from 47.0 pg/ml (IQR: 17.3 to 118.0 pg/ml) to 66.5 pg/ml (IQR: 26.5 to 155.5 pg/ml; $p = 0.004$) after exposure to DE). No changes in heart rate variability

Table 2 (continued)

Concentration of Diesel Exhaust (µg/m3)	Source	8 Hour TWA (µg/m^3)	Exposure Time (hours)	Times Exposed to Diesel Exhaust	Cohort Demographic	Exposure Method	Engine Classification	Health Impacts in Acute Exposures
348	Mills et al. (2011)	75	2	2	16 non-smoking healthy males (18–32 years old)	Exposure chamber	NS	Reduced vasodilation and increased blood pressure after DE exposure (mean ± SD: systolic blood pressure increased from 133 ± 3 to 145 ± 4 mmHg. Forearm blood flow vasodilation (~mean ± SEM, ml/100 ml tissue/ min) decreased after intra-brachial infusion of 1000 pmol/min bradykinin control vs exposed: 16.6 ± 2.2 vs 19.1 ± 2.6)). No changes to resting heart rate
350	Lundbäck et al. (2009)	43.75	1	1	12 non-smoking healthy males (21–30 years old)	Exposure chamber	NS[a]	Increased arterial stiffness (30 min after exposure, augmentation pressure- and augmentation index increased: (mean ± SEM, air vs DE exposure) -2.5 ± 0.7 vs −1.8 ± 0.8 (p = 0.01) and − 7.9 ± 2.2 vs −5.8 ± 2.7 ($p = 0.02$), respectively). No effect on heart rate or blood pressure

All studies diesel exhaust exposure levels below 400 µg/m^3 and no exposure occurred for more than three hours

SEM standard error of the mean, *SD* standard deviation, *C.I.* confidence interval, *IQR* interquartile range

~ Data obtained from graphical forms and thus are an approximation only

*= NS - Not Specified

[a]Volvo TD45, 4.5 L four cylinder 1991 engine model

[b]Turbocharged direct-injection 5.9-L Cummins 2002 B-series diesel engine (model 6BT5.9G6) and a 100-kW generator

[c]EPA Tier 3-compliant, 6.0 kW Coliseum GY6000 generator, with 406 cc Yanmar L 100 EE 4-stroke diesel generator

cell brushings (Clifford et al. 2017; Rider et al. 2016) and increased airway hyperactivity and obstruction in individuals with asthma or allergies (Hussain et al. 2012; Zhang et al. 2016a). Healthy individuals exposed for 30 min to 300 µg/m3 of DE reported significant irritation of the nose, throat and chest after exposure (Giles et al. 2018a). In comparison, heart rate was not affected (Lucking et al. 2011; Vieira et al. 2016). Some studies reported no changes in blood pressure after 30–60 min of exposure (Giles et al. 2018a, b; Lucking et al. 2011) and no changes in markers of inflammation and platelet activation (Giles et al. 2018a; Lucking et al. 2011); balance was not affected and no changes were found in central nervous system biomarkers (Cliff et al. 2016; Curran et al. 2018).

Exposures to DE at concentrations between 300 and 200 µg/m^3 resulted in similar health effects. Eye irritation was reported by 11 out of 18 healthy subjects exposed for up to three hours, and nose and throat irritation was diagnosed by a medical professional (Wierzbicka et al. 2014). Healthy subjects had decreased induced vasodilation (Barath et al. 2010), increased vasoconstriction (Peretz et al. 2008b) and increased blood pressure and inflammation after two hours of exposure (Cosselman et al. 2012; Tong et al. 2014) as well as altered gene expression in peripheral blood mononuclear cells (Peretz et al. 2007). In contrast, 60 min of exposure did not affect heart rate variability, systemic inflammation or blood pressure in 18 healthy male volunteers (Barath et al. 2010). No indications of oxidative stress was found in individuals with metabolic syndrome (Allen et al. 2009) and no changes in heart rate variability were found after two hours of exposure (Peretz et al. 2008a).

Studies examining concentrations of DE below 100 µg/m^3 report half the amount of vasoconstriction in comparison 200 µg/m^3 exposures completed in the same study, suggesting a linear dose–response although these levels were not significantly different to air exposures (Peretz et al. 2008b), increased airway inflammation in healthy subjects (Behndig et al. 2011), allergic inflammation and viral-induced immune responses in allergic rhinitics (Pawlak et al. 2016) and decreased lung function, increased airway acidification and increased respiratory inflammation in asthmatics exposed for two hours at exhaust concentrations up to 75 µg/m^3 (Zhang et al. 2009). No thrombotic effect was found in subjects with metabolic syndrome (Carlsten et al. 2008), no impact on heart rate was observed (Lucking et al. 2011; Peretz et al. 2008a; Tong et al. 2014), no impact on vasoconstriction was found (Lucking et al. 2011) and there was no evidence of respiratory epithelial cell damage in healthy, allergic or asthmatic individuals following exhaust exposure at 100 µg/m^3 for two hours (Behndig et al. 2015).

One study compared the health impact of exposure to DE with and without a DPF on 19 healthy volunteers. The use of a DPF decreased PM concentration from 320 to 7.2 µg/m^3. Study participants who were exposed to whole, unfiltered exhaust for one hour had increased thrombotic formation and reduced vasodilation. The use of a DPF negated the effects of exposure on vasodilation and decreased the thrombotic effect as well (Lucking et al. 2011).

Approximately 60% of acute human exposure studies used exhaust exposure concentrations between 250 and 350 µg/m^3, suggesting that this level of exposure is the concentration where an observable response is likely to occur using short exposure periods (Tong et al. 2014). At this level of exposure, health effects are noticeable by the participants themselves with reports of irritation to mucosal surfaces such as the nose, throat and eyes. Most studies examined the cardiovascular system (Steiner et al. 2016). As exposure levels decreased to 100 µg/m^3, reported health effects lowered in severity and more studies began reporting negative outcomes. Those that reported positive results mostly involved individuals with asthma or allergy, suggesting that they may be an at risk population that requires closer monitoring.

In addition, combining the results of both the occupational and acute human exposure studies shows potential to explore genetic alterations and DNA damage as potential biomarkers for disease and lung cancer risk after DE exposure. Rynning et al. found DNA damage in peripheral blood mononuclear cells associated with DE exposure (Rynning et al. 2019) and León-Mejía et al. found DNA damage of the buccal cheek cells and lymphocytes after continued DE exposure, with the amount of DNA damage correlating with years of service and thus years of exposure (León-Mejía et al. 2019). Thus, with more testing, there is potential to use either a cheek swap or a blood test to quantify DNA damage as a marker of increased cancer risk after DE exposure. Hypomethylation is another potential marker of DE exposure (Clifford et al. 2017), particularly hypomethylation and other changes to genes related to DNA damage responses such as p16, RASSF1A, and MGMT which are frequently found to be dysregulated in cancer (Zhang et al. 2016a, b). Alternatively, the plasma miRNA profile could be another marker as studies have found it to be significantly altered after DE exposure (Rynning et al. 2019; Rider et al. 2016), with several of the altered miRNA expressions such as miR-31–5 p, miR-20b-5p, miR-196b-5p, miR-4500 and miR-340 being associated with cancer (Rynning et al. 2019).

In Vivo (Animal Model) Exposure Studies

Approximately 74% of studies involving animal models focus on the respiratory and central nervous systems. A strength of animal studies is that long-term exposure can be compressed into the relatively short life span of experimental animals, meaning that lifetime exposures can be completed in a much shorter period of time than

in comparative human occupational studies. In addition, animal models can also be exposed to much higher concentrations than used in either occupational or acute studies involving human subjects. Thus, the majority of in vivo studies reviewed expose animals for a large range of exhaust concentrations over longer periods of time, including months or even years, which also represent greater proportions of their life expectancy, than human studies. Six in vivo studies examined the effects of acute exposure. Information on animal type and exposure methodology can be found in Tables 3 and 4.

Older Engine Technology The majority of in vivo exposure studies use old technology diesel engines and exposure concentrations vary greatly (between 50 and 3000 μg/m^3).

Studies that exposed animals to DE concentrations between 3000 and 2000 μg/m^3 for 1–12 weeks resulted in negative respiratory and neurological effects. A 3.2-fold greater DNA mutation frequency was found in the lungs of mice exposed for 12 weeks compared with air exposed controls suggesting greater cancer risk (Hashimoto et al. 2007), large increases in neuroinflammation were found in the brains of mice exposed for 4 weeks (Levesque et al. 2011b) and increased lung inflammation was found in mice exposed for less than a week, with allergic mice exhibiting greater symptoms (Stevens et al. 2008). In contrast, more recent studies exposing rats for one or 4 weeks to ~2000 μg/m^3 found only minor histopathological changes and inflammatory effects in the lungs (Magnusson et al. 2019) and minor oxidative stress in the brain (Valand et al. 2018).

Exposing mice to DE between the concentrations of 1000 and 2000 μg/m^3 has effects on the transcription of stress-related genes in the brain (Lung et al. 2014). Similar to an exposure concentration of 3000 μg/m^3, a 3.1-fold increase of DNA mutations was found in the lungs of mice exposed to 1000 μg/m^3 for 12 weeks, suggesting greater cancer risk (Hashimoto et al. 2007).

Studies exposing mice and rats to DE concentrations between 500 and 1000 μg/m^3 found oxidative stress and increased inflammation in the lungs of rats exposed to 950 μg/m^3 for < 1 week (Tsukue et al. 2010), increased neuroinflammation in mice exposed to 650 μg/m^3 for 4 weeks (similar to that found in 2000 μg/m^3 exposure concentrations) (Levesque et al. 2011b), increased flu severity in mice exposed to 500 μg/m^3 for < 2 weeks (Gowdy et al. 2010) and an increased effect of chemically induced arrhythmia in hypertensive rats exposed to 500 μg/m^3 for < 1 week (Hazari et al. 2015). Increased respiratory inflammation was found in allergic mice, but not healthy mice, exposed for < 1 week and the effects were lower than that found in mice exposed to 2000 μg/m^3, suggesting dose–response relationships in these particular outcomes (Stevens et al. 2008).

In vivo exposure to DE concentrations between 300 μg/m^3 and 100 μg/m^3 results in neurological effects including impaired neurogenesis in male mice exposed to 250 μg/m^3 for < one day (Coburn et al. 2018), increased neuroinflammation in mice exposed for 4 weeks to 173 and 149 μg/m^3 (Gerlofs-Nijland et al. 2010; Win-Shwe et al. 2008) and impact on object recognition ability in mice exposed to 129 μg/m^3 for 12 weeks (Win-Shwe et al. 2012). No impact was found on spatial learning abilities in mice exposed to 149 μg/m^3 for 4 weeks (Win-Shwe et al. 2008). Health impacts on other systems included increased respiratory inflammation in normal mice and increased respiratory inflammation and oxidative stress in asthmatic mice exposed to 200 μg/m^3 for 7 weeks or 169 μg/m^3 for 8 weeks, respectively (Bai et al. 2011; Tanaka et al. 2013a; Tanaka et al. 2013b), unfavourable changes in atherosclerotic plaques in mice exposed to 200 μg/m^3 for 7 weeks (Bai et al. 2011), changes in steroidogenesis in male rats exposed for 4 weeks to 149 μg/m^3 (Yamagishi et al. 2012), an increased effect of chemically induced arrhythmia in hypertensive rats exposed to 150 μg/m^3 for less than a week (Hazari et al. 2015), increased allergic symptoms in asthmatic mice exposed to 100 μg/m^3 for 12 weeks (Matsumoto et al. 2006) and increased oxidative stress in the lungs of rats exposed for 3 days to 100 μg/m^3, although no impact on respiratory inflammation was found (Tsukue et al. 2010).

Exposure studies that used DE concentrations below 100 μg/m^3 found mild increases in the effect of chemically induced arrhythmia in hypertensive rats exposed to 50 μg/m^3 for < 1 week (in comparison to exposure to 150 and 500 μg/m^3) (Hazari et al. 2015), increased oxidative stress in the lungs and minor impact on respiratory inflammation of rats exposed to 60 μg/m^3 for < 1 week (in comparison to exposure to 950 μg/m^3) (Tsukue et al. 2010), minor increases in respiratory inflammation in asthmatic mice exposed for 8 weeks to 39 μg/m^3 (in comparison to exposures to 169 μg/m^3) (Tanaka et al. 2013a), some impact on steroidogenesis in male rats exposed to 38 μg/m^3 for 8 weeks (Yamagishi et al. 2012) and no impact on object recognition in mice exposed to 47 μg/m^3 for 12 weeks or oxidative stress in mice exposed to 36 μg/m^3 for 8 weeks (Tanaka et al. 2013b; Win-Shwe et al. 2012).

New Engine Technology Seven in vivo studies exposed animals to the exhaust generated from new technology diesel engines. Exhaust concentrations never exceeded 200 μg/m^3 and all studies were published in the past 5 years. Rats exposed to 182 μg/m^3 for one and 4 weeks displayed changes in gene expression of the brain which suggests minor oxidative stress, although no histopathological effects were found and the differences compared to rats exposed to old technology exhaust at a concentration of 2000 μg/m^3 were minor (Valand et al. 2018). Magnusson et al. found

Table 3 Key experimental data from selected in vivo animal exposure studies using old technology DE

Concentration of Diesel Exhaust (µg/m^3)	Source	8 Hour TWA (µg/m^3)	Exposure Period	Animal	Engine Classification	Health Impacts in Older Technology Exhaust Exposures
38	Yamagishi et al. (2012)	23.8	5 h/day, 5 days/week, 1, 2 or 3 months	Rat	NS*	Some effects on steroidogenesis in male rats (increased plasma testosterone after 2 months exposure ($p < 0.05$), decreased plasma luteinizing hormone which regulates testosterone biosynthesis after 3 months ($p < 0.05$), no effect on hippocampus)
36	Tanaka et al. (2013b)	22.5	5 h/day, 5 day/week, 8 weeks	Mouse	NS	No effects of oxidative stress in lungs (8-OHdG expression used as marker) of healthy or asthmatic mice
39	Tanaka et al. (2013a)	24.4	5 h/day, 5 day/week, 8 weeks	Mouse	NS	Minor increases in respiratory inflammation in asthmatic mice, some indications of oxidative stress in the lungs (increased eosinophil number in bronchoalveolar lavage fluid (BALF), increased IFN-γ and IL-5 release ($p < 0.05$), increased myeloperoxidase levels in BALF ($p = <0.05$))
47	Win-Shwe et al. (2012)	29.4	5 h/day, 5 day/week, 3 months	Mouse	NS	No impact on object recognition
50	Hazari et al. (2015)	25	4 h/day, 1 or 5 days	Rat	NS	Mild increased effect of chemically induced arrhythmia (in comparison to 150 and 500 µg/m^3) (decreased dose of aconite needed to induce arrhythmia ($p < 0.05$))
60	Tsukue et al. (2010)	30	6 h/day, 1–7 days	Rat	NS	Impact on respiratory inflammation and increased oxidative stress (decreased macrophage levels ($p < 0.05$), increased release of 8-OHdG ($p < 0.001$) after 3 days of exposure)
82	Karthikeyan et al. (2013)	41	4 h/day, 1 and 3 days.	Rat	NS	Inflammation and increased oxidative stress in lungs and negative cardiovascular effects (increased number of BALF neutrophils, increased BALF levels of KC, MIP-1α and MCP-1 after single exposure, increased number of BALF macrophages after multiple exposures. Increased lung mRNA levels of *IL-6*, *TNF-α*, *HO-1* and *SOD2* after single exposure, increased *HO-1* and *iNOS* and decreased *SOD2* after multiple exposures. Increased levels of plasma endothelins). Greater effects than higher exhaust concentration without DPF usage

Table 3 (continued)

Concentration of Diesel Exhaust (µg/m^3)	Source	8 Hour TWA (µg/m^3)	Exposure Period	Animal	Engine Classification	Health Impacts in Older Technology Exhaust Exposures
100	Matsumoto et al. (2006)	87.5	7 h/day, 5 days/week, 12 weeks	Mouse	NS	Increased allergic symptoms in asthmatic mice (increased bronchoconstriction after methacholine challenge ($p < 0.001$), increased expression of *IL-4*, *IL-5*, *IL-13*, *MDC* and *RANTES* mRNA in lung tissue, increased release of IL-4 and RANTES in BALF ($p < 0.05$)), effects not prolonged with continuous exposure
100	Tsukue et al. (2010)	50	6 h/day, 1–7 days	Rat	NS	Increased respiratory oxidative stress (increased release of 8-OHdG after 3 days of exposure ($p < 0.001$)), no impact on respiratory inflammation
129	Win-Shwe et al. (2012)	80.6	5 h/day, 5 day/week, 3 months	Mouse	NS	Impact on object recognition (increased exploration time using novel object recognition test, increased inability to recognize familiar objects, decreased *CaMKIV* and *EAAT4* mRNA expression in hippocampus ($p < 0.05$))
149	Win-Shwe et al. (2008)	93.1	5 h/day, 5 days/week, 4 weeks	Mouse	NS	Increased neuroinflammation but no impact on spatial learning (increased expression of IL-1β and TNF-α mRNA in the hippocampus, increased expression of *NR1*, *NR2A* and *NR2B* mRNA in hippocampus ($p < 0.05$), no change in results for the Morris Water Maze Behaviour Test)
149	Yamagishi et al. (2012)	93.1	5 h/day, 5 days/week, 1, 2 or 3 months	Rat	NS	Effects on steroidogenesis in male rats (increased concentrations of plasma and testicular testosterone after 1 month or exposure and increased androstenedione concentrations in hippocampus after 1 month of exposure ($p < 0.05$))
150	Hazari et al. (2015)	75	4 h/day, 1 or 5 days	Rat	NS	Increased effect of chemically induced arrhythmia (decreased dose of aconite needed to induce arrhythmia ($p < 0.05$))
169	Tanaka et al. (2013b)	105.6	5 h/day, 5 day/week, 8 weeks	Mouse	NS	Increased oxidative stress in asthmatic mice compared to both air exposed and healthy control (increased levels of 8-OHdG in BALF)

Table 3 (continued)

Concentration of Diesel Exhaust (µg/m^3)	Source	8 Hour TWA (µg/m^3)	Exposure Period	Animal	Engine Classification	Health Impacts in Older Technology Exhaust Exposures
169	Tanaka et al. (2013a)	105.6	5 h/day, 5 day/week, 8 weeks	Mouse	NS	Increased respiratory inflammation and markers of oxidative stress in asthmatic mice (increased neutrophil, eosinophil and lymphocyte cell number in BALF, increased release of IL-5, IL-6, IL-13, MCP-1, TARC, MDC, Eotaxin and KC in BALF, increased levels of myeloperoxidase in BALF ($p < 0.05$))
173	Gerlofs-Nijland et al. (2010)	129.7	6 h/day, 5 days/week, 4 weeks	Mouse	NS	Increased neuroinflammation (increased expression of TNF-α and IL-1α in different regions of the brain ($p < 0.05$))
200	Bai et al. (2011)	150	6 h/day, 5 days/week, 7 weeks	Mouse	NS	Unfavourable changes in atherosclerotic plaques and increased respiratory inflammation (increased plaque lipid content, cellularity, foam cell content and smooth muscle content ($p < 0.05$), increased expression of oxidative stress markers iNOS, CD36 and nitrotyrosine and enhanced systemic lipid and DNA oxidation in plaques ($p < 0.05$). Increased levels of alveolar macrophages and increased number of alveolar macrophages positive for the presence of particles ($p < 0.01$))
250	Coburn et al. (2018)	187.5	6 h	Mouse	NS	Impaired neurogenesis and increased neuroinflammation in male mice (decreased cell proliferation in hippocampus and increased mRNA expression of TNFα and MDA in cerebral cortex and hippocampus ($p < 0.05$))
277	Karthikeyan et al. (2013)	138.5	4 h/day, 1 and 3 days.	Rat	NS	Inflammation and increased oxidative stress in lungs and negative cardiovascular effects (increased number of BALF neutrophils and increased BALF levels of KC after single exposure, increased number of BALF macrophages after multiple exposures. Increased lung mRNA levels of *IL-6*, *TNF-α*, *HO-1* and *SOD2* after single exposure, decreased *HO-1* and *SOD2* after multiple exposures. Increased levels of plasma endothelins)

Table 3 (continued)

Concentration of Diesel Exhaust (µg/m^3)	Source	8 Hour TWA (µg/m^3)	Exposure Period	Animal	Engine Classification	Health Impacts in Older Technology Exhaust Exposures
500	Gowdy et al. (2010)	250	4 h/day, 1–14 days	Mouse	NS	Increased flu severity, (increased viral titres of influenza A/HongKong/8/68 and increased BALF neutrophils at days 4 and 8 post infection and increased responsiveness to methacholine ($p < 0.05$). Increased mRNA expression of *INF-β* and *TNF-α* and decreased mRNA expression of *INF-γ* and *IL-12p40* in lungs ($p < 0.05$). Increased expression of TNF-α in BALF ($p < 0.05$))
500	Hazari et al. (2015)	250	4 h/day, 1 or 5 days	Rat	NS	Increased effect of chemically induced arrhythmia (decreased dose of aconite needed to induce arrhythmia ($p < 0.05$))
500	Stevens et al. (2008)	250	4 h/day, 4 days	Mouse	NS	Increased respiratory inflammation in allergic mice but not in healthy mice (increased number of neutrophils, eosinophils and lymphocytes in BALF ($p < 0.05$))
650	Levesque et al. (2011b)	325	4 h/day, 5 days/week, 4 weeks	Mouse	NS	Increased neuroinflammation(similar to that found in 2000 µg/m^3 exposures) (increased mRNA expression of *TNF-α*, *MIP-1α* and increased nitrotyrosine in whole brain homogenate, increased expression of IL-1β, IL-6, TNF-α, MIP-1, RAGE and IBA-1 after exposure in different regions of the brain ($p < 0.05$))
950	Tsukue et al. (2010)	712.5	6 h/day, 1–7 days	Rat	NS	Impact on respiratory inflammation (increased number of cells, increased levels of lymphocytes and decreased levels of macrophages in BALF ($p < 0.05$)
1000	Hashimoto et al. (2007)	1000	12 h/day, 7 days/week, 4, 12 and 24 weeks	Mouse	NS	A 3.1-fold increase in DNA mutation burden in the lungs of *gpt* delta transgenic mice (G:C → A:T transitions were the predominant *gpt* transgene mutation, no difference in mutation burden to the 3000 µg/m^3 exposures)
1700	Lung et al. (2014)	637.5	3 h/day, 5 days/week, 4 weeks	Mouse	NS	Impact on transcription of stress-related genes in the brain (AP-1 levels significantly decreased in the brain after DE exposure)
2000	Magnusson et al. (2019)	1500	6 h/day, 7 days or 6 h/day, 5 day/week, 4 weeks	Rat	EURO V (-DPF)	Minor histopathological changes and oxidative stress in lungs (focal mild emphysema and mild mononuclear infiltrate in the lungs, disrupted redox signalling pathways)

Table 3 (continued)

Concentration of Diesel Exhaust (µg/m^3)	Source	8 Hour TWA (µg/m^3)	Exposure Period	Animal	Engine Classification	Health Impacts in Older Technology Exhaust Exposures
2000	Valand et al. (2018)	1500	6 h/day, 7 days or 6 h/day, 5 day/week, 4 weeks	Rat	EURO V (-DPF)	Minor oxidative stress in brain (genes associated with oxidative stress and inflammation differentially expressed after DE exposure). No histopathological changes in frontal cortex or hippocampus. No differences in comparison to exposures with a DPF.
2000	Stevens et al. (2008)	1000	4 h/day, 4 days	Mouse	NS	Increased respiratory inflammation, allergic mice display greater symptoms (increased neutrophil numbers in BALF of normal mice ($p < 0.05$), increased neutrophil, eosinophil and lymphocyte numbers in BALF of allergic mice, IIL-6 release in BALF of allergic mice ($p < 0.01$), 49 enriched gene sets with 619 core genes were differentially expressed in normal mice after exposure to DE in comparison to air, 23 enriched gene sets with 412 core genes were differentially expressed in asthmatic mice after exposure to DE in comparison to air)
2000	Levesque et al. (2011b)	1000	4 h/day, 5 days/week, 4 weeks	Mouse	NS	Increase in neuroinflammation (increased mRNA expression of *TNF-α*, *MIP-1α* and increased nitrotyrosine in whole brain homogenate, increased expression of IL-1β, IL-6, TNF-α, MIP-1, RAGE and IBA-1 after exposure in different regions of the brain ($p < 0.05$))
3000	Hashimoto et al. (2007)	3000	12 h/day, 7 days/week, 4, 12 and 24 weeks	Mouse	NS	A 3.2-fold increase in DNA mutation burden in the lungs of *gpt* delta transgenic mice (G:C → A:T transitions were the predominant *gpt* transgene mutation, no difference in mutation burden to the 1000 µg/m^3 exposures)

**NS* not specified

Table 4 Key experimental data from selected in vivo animal exposure studies using new technology exhaust

Concentration of Diesel Exhaust (µg/m3)	Source	8 Hour TWA (µg/m^3)	Exposure Period	Animal	Engine Classification	Health Impacts in New Technology Exhaust Exposures
12	Bemis et al. (2015)	12	16 h/day, 5 days/week, 2 years.	Rat	US EPA 2007	No increase in micronucleation in blood samples
12	Hallberg et al. (2015)	12	16 h/day, 5 days/week, 2 years.	Rat	US EPA 2007	No DNA damage in either serum or lung tissue, no increase in serum oxidative stress markers
12	McDonald et al. (2015)	12	16 h/day, 5 days/week, 2 years.	Rat	US EPA 2007	No tumour development and mild negative histopathological change in the lungs (periacinar epithelial hyperplasia, bronchiolization, accumulation of macrophages, and periacinar interstitial fibrosis. Associated with the gas components of the exhaust)
12	Conklin and Kong (2015)	12	16 h/day,5 days/week, 2 years.	Rat	US EPA 2007	Mild inflammatory and cardiovascular effects in female rats (increased serum levels of IL-6 and sICAM-1 and decreased total non-high-density-lipoprotein cholesterol)
<100	Douki et al. (2018)	<37.5	3 Hours, 5 days/week, 3 weeks	Rat	EURO IV	Limited accumulation of lung DNA damage and effects of gene expression (limited induction of *γ-H2AX* and acrolein adducts and 171 genes dysregulated in comparison to air controls. Greater effects in exposures that used a DPF in comparison to exposures that did not)
170	Magnusson et al. (2019)	127.5	6 h/day, 7 days or 6 h/day, 5 day/week, 4 weeks	Rat	EURO V	Minor histopathological changes and oxidative stress in lungs (focal mild emphysema and mild mononuclear infiltrate in the lungs, disrupted redox signalling pathways, redox pathways more disrupted with the use of a DPF than without)
182	Valand et al. (2018)	136.5	6 h/day, 7 days or 6 h/day, 5 day/week, 4 weeks	Rat	EURO V	Minor oxidative stress in brain (genes associated with oxidative stress and inflammation differentially expressed after DE exposure). No histopathological changes in frontal cortex or hippocampus. No differences in comparison to exposures without a DPF.

*= *NS* not specified

minor respiratory inflammation and oxidative stress in the lungs of rats exposed to approximately 170 µg/m^3 for one and 4 weeks. No differences were found when compared to rats exposed to old technology exhaust at a concentration of 2000 µg/m^3 (Magnusson et al. 2019). Douki et al. found minor indications of accumulated lung DNA damage in rats exposed to less than 100 µg/m^3 for 3 weeks; however, effects were found to be worse with new technology exhaust when compared to old, suggesting that toxicity was associated with the ultrafine particulates and the gas phase of the exhaust (Douki et al. 2018). A series of studies exposed rats to 12 µg/m^3 of exhaust for 28–30 months and found only limited effects, including minor histopathological changes and mild increases in inflammatory and thrombotic markers; however, no damage to DNA was recorded and no increases in tumour development were found (Bemis et al. 2015; Conklin and Kong 2015; Hallberg et al. 2015; McDonald et al. 2015).

In in vivo exposure studies using old technology exhaust, exposure concentrations varied greatly with the highest exposures resulting in a range of health impacts to the respiratory, cardiovascular and neurological systems of mice and rats. The severity of these effects decreased as exposure decreased. Results were similar for new technology studies; however, the few studies available limit the conclusions that can be drawn. Once again, animals with conditions simulating asthma or allergy displayed worse symptoms and the study with the lowest exhaust exposure concentration that still reported exposure health impacts used asthmatic mice as subjects, highlighting potentially susceptible populations. Some studies also reported increased influenza severity in mice exposed to DE, which may highlight another susceptible population that was not found in the human exposure studies.

In Vitro (Cell Model) Exposure Studies

Most in vitro studies into the effects of DE exposure use DE particles collected on quartz filters and added directly to the media the cells are grown within (Zarcone et al. 2016). Using this approach to estimate the potential health consequences of exhaust exposure is limited as it ignores the health consequences of the exhaust gases entirely. In addition, the particles collected on the filter agglomerate, sticking together to generate an artificial particle spectrum made of larger particles, often removing the ultrafine particles from the sample and thus from the subsequent analysis of exposure health effects (Morin et al. 2008). This approach often underestimates health consequences of exposure and over 16 times higher concentrations of particles are needed to generate the same health consequences as exposure to whole exhaust (Lichtveld et al. 2012). All in vitro studies included in this review use whole exhaust instead of pre-collected particles and focus on the damage caused to the respiratory epithelium, either using primary human epithelial cells or the alveolar carcinoma cell line A549. All cells were grown at an air–liquid interface, exposing one side of the cell model directly to the diluted DE (Tables 5 and 6).

Older Engine Technology Studies exposing cells to old technology diesel engine exhaust have mostly focussed on cell damage, oxidative stress and inflammatory responses. A549 cells exposed to 1600 µg/m^{3}at air–liquid interface displayed inhibited proliferation and increased oxidative stress (Okubo et al. 2015). The same cells exposed to exhaust after the use of a DPF, at a concentration of 470 µg/m^3, exhibited suppressed immune reactivity in comparison to air exposed controls. Oxidative stress was decreased in comparison to the DE exposure concentration of 1600 µg/m^3; however, the decreased immune response after exposure was only found in those cells exposed to the DPF-equipped exhaust (Okubo et al. 2015). A549 cells exposed to 1300 µg/m^3 at air–liquid interface displayed increased cell death and increased oxidative stress (Kooter et al. 2013), while differentiated primary human bronchial airway epithelium grown at air–liquid interface and exposed to DE at a concentration of 850 µg/m^3 displayed increased oxidative stress and increased PAH adduct formation but no loss of viability (Hawley et al. 2014).

Three studies exposed differentiated primary human airway epithelial cells collected from healthy volunteers and volunteers with COPD to a range of exhaust concentrations and types (Zarcone et al. 2016, 2017, 2018). In a study that used old technology exhaust, Zarcone et al. (2016) found that exposing the cells to ~1200 µg/m^3 induced the production of inflammatory markers, oxidative stress, cellular death and increased permeability after 150 min of exposure. At 430 µg/m^3, they found increased oxidative stress after 150 min and increased permeability after 375 min. At 140 µg/m^3, only decreased permeability was recorded (Zarcone et al. 2016).

New Engine Technology Only three in vitro exposure studies were found that examined new technology DE exposure. Exposure to 1500 µg/m^3 for 60 min induced oxidative stress and decreased the defence response to infection, although no cellular death occurred (Zarcone et al. 2017). Primary human airway epithelial cells exposed to three different, much lower, exhaust concentrations found that the lowest concentration (34 µg/m^3) had no impact on healthy cells, the second lowest concentration (82 µg/m^3) increased oxidative stress in healthy cells and the highest concentration (206 µg/m^3) increased oxidative stress in healthy cells and

Table 5 Key experimental data from selected in vitro exposure studies using old technology exhaust

Concentration of Diesel Exhaust µg/m^3)	Source	8 Hour TWA (µg/m^3)	Exposure Period (Minutes)	Cohort Demographic	Engine Classification	Old Technology Exhaust
140	Zarcone et al. (2016)	17.5–109.38	60–375	Mucociliary differentiated primary bronchial epithelial cells obtained from normal volunteers	NS	Decreased permeability (higher TEER measurement compared to air controls ($p < 0.01$))
430	Zarcone et al. (2016)	53.75–335.93	60–375	Mucociliary differentiated primary bronchial epithelial cells obtained from normal volunteers	NS	Increased oxidative stress and permeability (increased NQO1 mRNA expression and lower TEER measurement compared to air controls ($p < 0.05$))
470	Okubo et al. (2015)	19.58–117.5	20–120	Alveolar basal epithelial cell line A549	NS	Suppressed immune response and increased oxidative stress (decreased release of IL-8, *HO-1* mRNA expression levels increased ($p < 0.001$))
850	Hawley et al. (2014)	8.86–106.29	5–60	Mucociliary differentiated primary bronchial epithelial cells obtained from normal volunteers	NS	Increased oxidative stress and increased cellular responses to diesel pollutants (PAHs) (increased mRNA expression of *HO-1* and *CYP1A1* ($p < 0.01$)). No loss of viability
1200	Zarcone et al. (2016)	150–937.5	60–375	Mucociliary differentiated primary bronchial epithelial cells obtained from normal volunteers	NS	Increased inflammation, cell death, permeability and oxidative stress (increased *IL-8*, *CHOP*, *GADD34*, *HMOX1* and *NQO1* mRNA expression, increased LDH release, decreased TEER measurement ($p < 0.05$))
1300	Kooter et al. (2013)	975	90	Alveolar basal epithelial cell line A549	EURO III	Increased cell death and increased oxidative stress (decreased Alamar Blue concentration, decreased GSH/GSSG ratio and increased HO-1 levels)
1600	Okubo et al. (2015)	66.7–400	20–120	Mucociliary differentiated primary bronchial epithelial cells obtained from normal volunteers	NS	Inhibited cell proliferation and increased oxidative stress (*HO-1* mRNA and protein expression levels increased ($p < 0.001$))

All studies human airway epithelial cells and use air–liquid interface cultures

**NS* not specified

Table 6 Key experimental data from selected in vitro exposure studies using new technology exhaust

Concentration of Diesel Exhaust (μg/m^3)	Source	8 Hour TWA (μg/m^3)	Exposure Period (minutes)	Cohort Demographic	Engine Classification	New Technology Exhaust
34	Zarcone et al. (2018)	25.5	360	Mucociliary differentiated primary bronchial epithelial cells obtained from both normal and COPD patients	EURO V	No effect on oxidative stress levels
35	Hawley et al. (2014)	0.37–4.41	5–60	Mucociliary differentiated primary bronchial epithelial cells obtained from normal volunteers	NS*	Increased oxidative stress and increased cellular responses to diesel pollutants (PAHs) (increased mRNA expression of *HO-1* and *CYP1A1* ($p < 0.01$)). No loss of viability
82	Zarcone et al. (2018)	61.5	360	Mucociliary differentiated primary bronchial epithelial cells obtained from both normal and COPD patients	EURO V	Increased oxidative stress (increased mRNA expression of *HMOX1* and *NQO1* 90 min post exposure ($p < 0.01$))
206	Zarcone et al. (2018)	64.37–154.5	150–360	Mucociliary differentiated primary bronchial epithelial cells obtained from both normal and COPD patients	EURO V	Increased oxidative stress and decreased defence response to infection in COPD-derived cells (increased mRNA expression of *HMOX1* and *NQO1* 90 min post exposure ($p < 0.01$), increased IL-8 mRNA expression and decreased BiP mRNA expression in NTHI-infected COPD-derived cells after DE exposure in comparison to air exposed controls)
1500	Zarcone et al. (2017)	187.5	60	Mucociliary differentiated primary bronchial epithelial cells obtained from both normal and COPD patients	TIER 4	Increased oxidative stress and decreased defence response to infection (increased mRNA expression of *HMOX1*, *CHOP*, *GADD34* and *IL-8* and decreased NTHI-induced mRNA expression of *BiP* and *S100A7* ($p < 0.05$))

All studies human airway epithelial cells and use air–liquid interface cultures

**NS* not specified

decreased host defence in COPD-derived cells (Zarcone et al. 2018). Differentiated primary human airway epithelial cells exposed to a DE concentration of 35.3 µg/m^3 found increased oxidative stress and increased PAH adduct formation. No difference in health effects was observed between new technology exhaust and old technology exhaust at a concentration of 800 µg/m^3 (Hawley et al. 2014).

Occupational Exposure Limits and Their Applicability

The Australian Institute of Occupational Hygienists recommends a DE occupational exposure limit of 100 µg/m^3 as a time weighted average over 8 h, measured as elemental carbon (AIOH 2017). In America, the DE exposure limit in a non-coal mining setting was set in 2008 at 160 µg/m^3 total carbon (MSHA 2016). However, there is no particle mass exposure limit set for non-mining settings (OSHA 2013). As of 2019, the European Union have introduced occupational DE exposure limits of 50 µg/m^3 EC, to be put into effect in 2023 in non-mining settings and 2026 in a mining setting (EU 2004). Previous DE exposure health effect reviews have recommended an occupational exposure limit of 100 µg/m^3 of diesel PM in total, which is equivalent to approximately 75 µg/m^3 EC (Taxell and Santonen 2017). Using the acute human studies reviewed in this report as the basis for the cross comparison, this limit is accurate for reducing the health effects of short-term exposure in healthy workers. However, this limit fails to take the safety and comfort of workers with asthma or allergy into account and is far above occupational exhaust concentrations where studies found significantly increased lung cancer risk. Previously published reviews recommended the lower occupational exposure threshold of 50 µg/m^3 of respirable EC (approximately 67 µg/m^3 of PM) in order to reduce lung cancer risk (Möhner and Wendt 2017). This current review, based on the acute human exposure studies and the occupational exposure studies, suggests a limit below 50 µg/m^3 of PM, approximately 35 µg/m^3 EC, would be more suitable. This level is below the exposure concentrations where effects were observed among asthmatics and below the concentrations that found the higher lung cancer risks (an increase of 38 (19–97, 95% confidence interval) lung cancer deaths per 1000 male workers (Peters et al. 2017) and a significant increase in DNA damage and dysregulation of microRNAs, some of which were associated with carcinogenesis (Rynning et al. 2019)). In addition, this limit is supported by in vivo exposure studies, where exposure concentrations at 50 µg/m^3 only resulted in mild health effects.

However, it should be noted that exposure limits based on both the mass of EC, as well as the mass of total PM, are limited in their long-term applicability. In order to meet the suggested 50 µg/m^3 PM occupational limit, most if not all diesel equipment must be fitted with exhaust after-treatment devices, including a DPF. Diesel particulate filters remove particles from the exhaust; however, they preferentially select for EC above other particle types (Hawley et al. 2014; Khalek et al. 2011) skewing the exhaust output and eliminating EC as a predictive measure for overall exhaust exposure, making any occupational limits based on EC unreliable.

Occupational limits based on particle mass have their own drawbacks. Evidence is accumulating that it is particle size and particle number that contribute more towards health impact than total particle mass (Cauda et al. 2012; Hawley et al. 2014; Ramachandran et al. 2005), making occupational limits based on mass, without accounting for particle size and number, a questionable decision. The latest European Emission Standards take this into account and have set limits for both particle mass and particle number (EU-Commission 2011).

In addition, multiple studies published in the last decade are reporting little to no change in health impacts after the use of a DPF. In in vivo and in vitro exhaust exposure studies that compare exposure health effects before and after the use of a DPF, few to no decreases in health impact are found (Douki et al. 2018; Gioda et al. 2016; Hawley et al. 2014; Karthikeyan et al. 2013; Magnusson et al. 2019; Okubo et al. 2015; Steiner et al. 2013; Valand et al. 2018) with only a few adverse cardiovascular events, including thrombosis and vasoconstriction, being decreased or prevented in an acute human exposure study (Lucking et al. 2011). Diesel particulate filters remove more than 90% by mass of particles from the exhaust (Hawley et al. 2014; Lucking et al. 2011; Magnusson et al. 2019; Valand et al. 2018). However, they cannot be 100% efficient given pressure drop constraints of the system, and therefore some particles (generally in the smaller size ranges) will pass through the DPF. Also at the operating temperatures of a DPF, many particles (such as PAHs) are liquid and can migrate through the filter and be resuspended (PubChem; Hawley et al. 2014; Khalek et al. 2011). Indeed PAH can melt as low as 80 °C and boil as low as 200 °C, both of which are well below typical exhaust temperatures (PubChem). The addition of after-treatment devices, such as a DOC, may even generate additional nitro-PAHs (Carrara and Niessner 2011; Inomata et al. 2015). This suggests that either the exhaust gases are having a greater effect on health than previously thought or that ultrafine particles, and the toxic chemicals potentially adsorbed to their surface, are responsible for the majority of health impacts caused by diesel PM (Douki et al. 2018; Hawley et al. 2014; Karthikeyan et al. 2013; Tanaka et al. 2013b). Thus, using occupational limits based on particle mass, an exhaust exposure that was over the limit where negative health consequences occur would read as under with the use of a DPF,

and yet the DPF would have little to no impact on decreasing the health impacts on an exposed worker.

Limits on particle number should also be addressed. Studies have found NO_x to be a reliable indicator of DE exposure, as long as the majority of sources contributing to the NO_x concentrations are diesel engines (Hedmer et al. 2017; Taxell and Santonen 2017). Equipment that measure NO_x concentrations are also less expensive than the equipment needed for EC measurement (Hedmer et al. 2017) and thus an additional occupational limit based on NO_x should not prove to be an expensive burden on industry. However, a more thorough review on the health effects of NO_x and its applicability as a DE exposure predictive measurement should be conducted before any sort of limit is put into effect. In future, more research needs to be conducted on the health effects of exposure to new technology diesel engine exhaust and further occupational studies need to be based on the possible health outcomes of the increasing application of new technology engines in industry.

Limitations

The majority of literature was sourced from PubMed using strict search criteria and thus it is possible that relevant studies were missed. Studies were only included if they were written in English and thus relevant studies in other languages were also excluded. This review focussed on studies relevant to occupational exposure settings and thus studies that used exhaust concentrations not relevant to occupational exposure conditions were not included.

The studies included in this review use a wide variety of engine types with varying emission classifications and after-treatment devices. Details of engine specifications and settings used during the exposures are limited, if they are reported at all. This, combined with the wide range of exposure outcomes measured, makes firm conclusions difficult for setting occupational DE exposure limits. Consistency in experimental designs and strict guidelines for reporting engine specifications and settings in DE exposure research would help immensely in solving this issue.

Many of the occupational exposure and acute human exposure studies also use exclusively male subjects and more research needs to be done to verify that occupational DE exposure has similar health impacts in both men and women. The few animal studies that compare both sexes often show differences in response between males and females (Coburn et al. 2018; McDonald et al. 2015; Conklin and Kong 2015). There is insufficient evidence to assess whether these differences also exist in humans. In addition, very few studies exist that exposed human, animal or tissue to "new technology" exhaust and thus further research is needed to confirm the findings of this review. Future studies in DE exposure effects should concentrate on using newer technology engines and after-treatment devices in order to consolidate the health effects of exposure to "new technology" engine exhaust before it becomes more widely used in an occupational setting.

Conclusion

In conclusion, an occupational exposure limit of 100 µg/m^3 is too high as it does not take increased lung cancer risk caused by high levels of DE exposure into effect. A limit of 50 µg/m^3 is more appropriate if lung cancer risk and the effects of exposure on workers with asthma, allergy and respiratory disease are accounted for. An occupational exposure limit based on EC is not appropriate as after-treatment devices preferentially remove it from the exhaust, making it an unreliable indicator of exhaust exposure. After-treatment devices also make occupational limits based on particle mass unreliable at best and additional limits, such as ones based on particle number or NO_x concentrations, are needed in order for occupational exhaust exposures to be reliably monitored.

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Availability of data and material All data and citations used within this review are available online.

Compliance with Ethical Standards

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References

Abe S, Takizawa H, Sugawara I, Kudoh S (2000) Diesel exhaust (DE)–induced cytokine expression in human bronchial epithelial cells. Am J Respir Cell Mol Biol 22:296–303. https://doi.org/10.1165/ajrcmb.22.3.3711

AIOH, Australian Institute of Occupational Hygienists (2017) Diesel particulate matter and occupational health issues- position paper

Allen J, Trenga CA, Peretz A, Sullivan JH, Carlsten CC, Kaufman JD (2009) Effect of diesel exhaust inhalation on antioxidant and oxidative stress responses in adults with metabolic syndrome. Inhal Toxicol 21:1061–1067. https://doi.org/10.3109/08958370902721424

Attfield MD et al (2012) The diesel exhaust in miners study: a cohort mortality study with emphasis on lung cancer. J Natl Cancer Inst 104:869–883. https://doi.org/10.1093/jnci/djs035

Bai N et al (2011) Changes in atherosclerotic plaques induced by inhalation of diesel exhaust. Atherosclerosis 216:299–306. https://doi.org/10.1016/j.atherosclerosis.2011.02.019

Barath S et al (2010) Impaired vascular function after exposure to diesel exhaust generated at urban transient running conditions. Part Fibre Toxicol (7):19–19. https://doi.org/10.1186/1743-8977-7-19

Bassig BA et al (2017) Occupational exposure to diesel engine exhaust and alterations in immune/inflammatory markers: a cross-sectional molecular epidemiology study in China. Carcinogenesis 38:1104–1111. https://doi.org/10.1093/carcin/bgx081

Behndig AF 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. https://doi.org/10.1136/thx.2010.140053

Behndig AF et al (2015) Effects of controlled diesel exhaust exposure on apoptosis and proliferation markers in bronchial epithelium – an in vivo bronchoscopy study on asthmatics, rhinitics and healthy subjects. BMC Pulm Med 15:99–99. https://doi.org/10.1186/s12890-015-0096-x

Bemis JC, Torous DK, Dertinger SD (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 141-171

Benbrahim-Tallaa L et al (2012) Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. Lancet Oncol 13:663–664. https://doi.org/10.1016/S1470-2045(12)70280-2

Bonassi S, El-Zein R, Bolognesi C, Fenech M (2011) Micronuclei frequency in peripheral blood lymphocytes and cancer risk: evidence from human studies. Mutagenesis 26:93–100. https://doi.org/10.1093/mutage/geq075

Brook RD et al (2010) Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association American Heart Association. Circulation 121:2331–2378. https://doi.org/10.1161/CIR.0b013e3181dbece1

Bünger J et al (2000) Cytotoxic and mutagenic effects, particle size and concentration analysis of diesel engine emissions using biodiesel and petrol diesel as fuel. Arch Toxicol 74:490–498. https://doi.org/10.1007/s002040000155

Carlsten C, Kaufman JD, Trenga CA, Allen J, Peretz A, Sullivan JH (2008) Thrombotic markers in metabolic syndrome subjects exposed to diesel exhaust. Inhal Toxicol 20:917–921. https://doi.org/10.1080/08958370802074908

Carrara M, Niessner R (2011) Impact of a NO2-regenerated diesel particulate filter on PAH and NPAH emissions from an EURO IV heavy duty engine. J Environ Monit 13:3373–3379. https://doi.org/10.1039/C1EM10573F

Cauda EG, Ku BK, Miller AL, Barone TL (2012) Toward developing a new occupational exposure metric approach for characterization of diesel aerosols. Aerosol Sci Technol 46:1370–1381. https://doi.org/10.1080/02786826.2012.715781

Cliff R, Curran J, Hirota JA, Brauer M, Feldman H, Carlsten C (2016) Effect of diesel exhaust inhalation on blood markers of inflammation and neurotoxicity: a controlled, blinded crossover study. Inhal Toxicol 28:145–153. https://doi.org/10.3109/08958378.2016.1145770

Clifford RL et al (2017) Inhalation of diesel exhaust and allergen alters human bronchial epithelium DNA methylation. J Allergy Clin Immunol 139:112–121. https://doi.org/10.1016/j.jaci.2016.03.046

Coburn JL, Cole TB, Dao KT, Costa LG (2018) Acute exposure to diesel exhaust impairs adult neurogenesis in mice: prominence in males and protective effect of pioglitazone. Arch Toxicol 92:1815–1829. https://doi.org/10.1007/s00204-018-2180-5

Conklin DJ, Kong M (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

Cosselman KE et al (2012) Blood pressure response to controlled diesel exhaust exposure in human subjects. Hypertension 59:943–948. https://doi.org/10.1161/HYPERTENSIONAHA.111.186593

Curran J, Cliff R, Sinnen N, Koehle M, Carlsten C (2018) Acute diesel exhaust exposure and postural stability: a controlled crossover experiment. J Occup Med Toxicol 13:2. https://doi.org/10.1186/s12995-017-0182-5

Dai Y et al (2018) Occupational exposure to diesel engine exhaust and serum cytokine levels. Environ Mol Mutagen 59:144–150. https://doi.org/10.1002/em.22142

Dallmann T, Menon A (2016) Technology pathways for diesel engines used in non-road vehicles and equipment. International Council on Clean Transportation (ICCT), Washington, DC

Douki T et al (2018) Comparative study of diesel and biodiesel exhausts on lung oxidative stress and genotoxicity in rats. Environ Pollut 235:514–524. https://doi.org/10.1016/j.envpol.2017.12.077

EU-Commission, European Union-Commission (2011) Commission Regulation (EU) No 582/2011

European Union (2004) Directive 2004/37/EC of the European Parliament and of the council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. Eur Union, 47:50–76

Evans KA, Halterman JS, Hopke PK, Fagnano M, Rich DQ (2014) Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbation among urban children. Environ Res 129:11–19. https://doi.org/10.1016/j.envres.2013.12.001

Fontaras G et al (2009) Effects of biodiesel on passenger car fuel consumption, regulated and non-regulated pollutant emissions over legislated and real-world driving cycles. Fuel 88:1608–1617. https://doi.org/10.1016/j.fuel.2009.02.011

Gerlofs-Nijland ME, van Berlo D, Cassee FR, Schins RPF, Wang K, Campbell A (2010) Effect of prolonged exposure to diesel engine exhaust on proinflammatory markers in different regions of the rat brain. Part Fibre Toxicol 7:12–12. https://doi.org/10.1186/1743-8977-7-12

Giles LV, Carlsten C, Koehle MS (2018a) The pulmonary and autonomic effects of high-intensity and low-intensity exercise in diesel exhaust. Environ Health 17:87–87. https://doi.org/10.1186/s12940-018-0434-6

Giles LV, Tebbutt SJ, Carlsten C, Koehle MS (2018b) The effect of low and high-intensity cycling in diesel exhaust on flow-mediated dilation, circulating NOx, endothelin-1 and blood pressure. PLoS One 13:e0192419. https://doi.org/10.1371/journal.pone.0192419

Gioda A, Rodríguez-Cotto RI, Amaral BS, Encarnación-Medina J, Ortiz-Martínez MG, Jiménez-Vélez BD (2016) Biodiesel from soybean promotes cell proliferation in vitro. Toxicol In Vitro 34:283–288. https://doi.org/10.1016/j.tiv.2016.05.004

Gowdy KM, Krantz QT, King C, Boykin E, Jaspers I, Linak WP, Gilmour MI (2010) Role of oxidative stress on diesel-enhanced influenza infection in mice. Part Fibre Toxicol 7:34–34. https://doi.org/10.1186/1743-8977-7-34

Hallberg LM, Ward JB, Hernandez C, Ameredes BT, Wickliffe JK (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 AH et al (2007) Mutations in the lungs of gpt delta transgenic mice following inhalation of diesel exhaust. Environ Mol Mutagen 48:682–693. https://doi.org/10.1002/em.20335

Hawley B, L'Orange C, Olsen DB, Marchese AJ, Volckens J (2014) Oxidative stress and aromatic hydrocarbon response of human bronchial epithelial cells exposed to petro- or biodiesel exhaust

treated with a diesel particulate filter. Toxicol Sci 141:505–514. https://doi.org/10.1093/toxsci/kfu147

Hazari MS, Haykal-Coates N, Winsett DW, King C, Krantz QT, Gilmour MI, Farraj AK (2015) The effects of B0, B20, and B100 soy biodiesel exhaust on aconitine-induced cardiac arrhythmia in spontaneously hypertensive rats. Inhal Toxicol 27:557–563. https://doi.org/10.3109/08958378.2015.1054967

Hedmer M, Tinnerberg H, Li H, Albin M, Broberg K, Wierzbicka A (2017) Diesel exhaust exposure assessment among tunnel construction workers—correlations between nitrogen dioxide, respirable elemental carbon, and particle number. Ann Work Expo Health 61:539–553. https://doi.org/10.1093/annweh/wxx024

Heidari Nejad S et al (2015) The effect of diesel exhaust exposure on blood–brain barrier integrity and function in a murine model. J Appl Toxicol 35:41–47. https://doi.org/10.1002/jat.2985

Hemmingsen JG, Møller P, Nøjgaard JK, Roursgaard M, Loft S (2011) Oxidative stress, genotoxicity, and vascular cell adhesion molecule expression in cells exposed to particulate matter from combustion of conventional diesel and methyl Ester biodiesel blends. Environ Sci Technol 45:8545–8551. https://doi.org/10.1021/es200956p

Hesterberg TW, Long CM, Sax SN, Lapin CA, McClellan RO, Bunn WB, Valberg PA (2011) Particulate matter in new technology diesel exhaust (NTDE) is quantitatively and qualitatively very different from that found in traditional diesel exhaust (TDE). J Air Waste Manage Assoc 61:894–913. https://doi.org/10.1080/10473289.2011.599277

Hu S et al (2013) Emissions of polycyclic aromatic hydrocarbons (PAHs) and nitro-PAHs from heavy-duty diesel vehicles with DPF and SCR. J Air Waste Manag Assoc 63:984–996

Hussain S et al (2012) Controlled exposure to diesel exhaust causes increased nitrite in exhaled breath condensate among subjects with asthma. J Occup Environ Med 54:1186–1191. https://doi.org/10.1097/JOM.0b013e31826bb64c

IARC, International Agency for Research on Cancer (2018) Agents classified by the IARC monographs, Vols. 1–120. International Agency for the Research on Cancer. http://monographs.iarc.fr/ENG/Classification/. Accessed 21 Feb 2018

Inomata S, Fushimi A, Sato K, Fujitani Y, Yamada H (2015) 4-Nitrophenol, 1-nitropyrene, and 9-nitroanthracene emissions in exhaust particles from diesel vehicles with different exhaust gas treatments. Atmos Environ 110:93–102. https://doi.org/10.1016/j.atmosenv.2015.03.043

Jiang R, Jones MJ, Sava F, Kobor MS, Carlsten C (2014) Short-term diesel exhaust inhalation in a controlled human crossover study is associated with changes in DNA methylation of circulating mononuclear cells in asthmatics. Part Fibre Toxicol 11:71–71. https://doi.org/10.1186/s12989-014-0071-3

Kachuri L, Villeneuve PJ, Parent M-É, Johnson KC, Canadian Cancer Registries Epidemiology Research G, Harris SA (2016) Workplace exposure to diesel and gasoline engine exhausts and the risk of colorectal cancer in Canadian men. Environ Health 15:4–4. https://doi.org/10.1186/s12940-016-0088-1

Karavalakis G, Stournas S, Bakeas E (2009) Light vehicle regulated and unregulated emissions from different biodiesels. Sci Total Environ 407:3338–3346. https://doi.org/10.1016/j.scitotenv.2008.12.063

Karthikeyan S et al (2013) Nitrogen dioxide and ultrafine particles dominate the biological effects of inhaled diesel exhaust treated by a catalyzed diesel particulate filter. Toxicol Sci 135:437–450. https://doi.org/10.1093/toxsci/kft162

Kavanagh T (2014) International fuel quality standards and their implications for Australian standards. Australian Government, Department of the Environment,

Khalek IA, Bougher TL, Merritt PM, Zielinska B (2011) Regulated and unregulated emissions from highway heavy-duty diesel engines complying with U.S. Environmental Protection Agency 2007 emissions standards. J Air Waste Manage Assoc 61:427–442. https://doi.org/10.3155/1047-3289.61.4.427

Kisin ER, Shi XC, Keane MJ, Bugarski AB, Shvedova AA (2013) Mutagenicity of biodiesel or diesel exhaust particles and the effect of engine operating conditions. J Environ Eng Ecol Sci 2. https://doi.org/10.7243/2050-1323-2-3

Kittelson D, Watts W, Johnson J (2002) Diesel aerosol sampling methodology–CRC E-43 final report. Coordinating Research Council

Kooter IM, Alblas MJ, Jedynska AD, Steenhof M, Houtzager MMG, Ras MV (2013) Alveolar epithelial cells (A549) exposed at the air–liquid interface to diesel exhaust: first study in TNO's powertrain test center. Toxicol in Vitro 27:2342–2349. https://doi.org/10.1016/j.tiv.2013.10.007

Larcombe AN, Phan JA, Kicic A, Perks KL, Mead-Hunter R, Mullins BJ (2014) Route of exposure alters inflammation and lung function responses to diesel exhaust. Inhal Toxicol 26:409–418. https://doi.org/10.3109/08958378.2014.909910

Larcombe AN, Kicic A, Mullins BJ, Knothe G (2015) Biodiesel exhaust: the need for a systematic approach to health effects research. Respirology 20:1034–1045. https://doi.org/10.1111/resp.12587

León-Mejía G et al (2019) Cytotoxic and genotoxic effects in mechanics occupationally exposed to diesel engine exhaust. Ecotoxicol Environ Saf 171:264–273. https://doi.org/10.1016/j.ecoenv.2018.12.067

Levesque S, Surace MJ, McDonald JD, Block ML (2011a) Air pollution & the brain: subchronic diesel exhaust exposure causes neuroinflammation and elevates early markers of neurodegenerative disease. J Neuroinflammation 8:105–105. https://doi.org/10.1186/1742-2094-8-105

Levesque S et al (2011b) Diesel exhaust activates and primes microglia: air pollution, neuroinflammation, and regulation of dopaminergic neurotoxicity. Environ Health Perspect 119:1149–1155. https://doi.org/10.1289/ehp.1002986

Lichtveld KM, Ebersviller SM, Sexton KG, Vizuete W, Jaspers I, Jeffries HE (2012) In vitro exposures in diesel exhaust atmospheres: resuspension of PM from filters versus direct deposition of PM from air. Environ Sci Technol 46:9062–9070. https://doi.org/10.1021/es301431s

Lucking AJ et al (2011) Particle traps prevent adverse vascular and prothrombotic effects of diesel engine exhaust inhalation in men. Circulation 123:1721–1728. https://doi.org/10.1161/circulationaha.110.987263

Lundbäck M et al (2009) Experimental exposure to diesel exhaust increases arterial stiffness in man. Part Fibre Toxicol 6:7. https://doi.org/10.1186/1743-8977-6-7

Lung S, Cassee FR, Gosens I, Campbell A (2014) Brain suppression of AP-1 by inhaled diesel exhaust and reversal by cerium oxide nanoparticles. Inhal Toxicol 26:636–641. https://doi.org/10.3109/08958378.2014.948651

Magnusson P et al (2019) Lung effects of 7- and 28-day inhalation exposure of rats to emissions from 1st and 2nd generation biodiesel fuels with and without particle filter – the FuelHealth project. Environ Toxicol Pharmacol 67:8–20. https://doi.org/10.1016/j.etap.2019.01.005

Matsumoto A, Hiramatsu K, Li Y, Azuma A, Kudoh S, Takizawa H, Sugawara I (2006) Repeated exposure to low-dose diesel exhaust after allergen challenge exaggerates asthmatic responses in mice. Clin Immunol 121:227–235. https://doi.org/10.1016/j.clim.2006.08.003

McDonald JD et al (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 184:44

Mills NL et al (2007) Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. N Engl J Med 357:1075–1082. https://doi.org/10.1056/NEJMoa066314

Mills NL et al (2011) Combustion-derived nanoparticulate induces the adverse vascular effects of diesel exhaust inhalation. Eur Heart J 32:2660–2671. https://doi.org/10.1093/eurheartj/ehr195

Möhner M, Wendt A (2017) A critical review of the relationship between occupational exposure to diesel emissions and lung cancer risk. Crit Rev Toxicol 47:185–224. https://doi.org/10.1080/10408444.2016.1266598

Morin J-P et al (2008) Prevalidation of in vitro continuous flow exposure systems as alternatives to in vivo inhalation safety evaluation experimentations: outcome from MAAPHRI-PCRD5 research program. Exp Toxicol Pathol 60:195–205. https://doi.org/10.1016/j.etp.2008.01.007

MSHA, Mine Safety and Health Administration (2016) Exposure of underground miners to diesel exhaust. Document: 81 FR 36826

Mullins BJ, Kicic A, Ling K-M, Mead-Hunter R, Larcombe AN (2016) Biodiesel exhaust–induced cytotoxicity and proinflammatory mediator production in human airway epithelial cells. Environ Toxicol 31:44–57. https://doi.org/10.1002/tox.22020

Niu Y et al (2018) Exposure characterization and estimation of benchmark dose for cancer biomarkers in an occupational cohort of diesel engine testers. J Expo Sci Environ Epidemiol 28:579–588. https://doi.org/10.1038/s41370-018-0061-x

Oberdörster G, Celein RM, Ferin J, Weiss B (1995) Association of particulate air pollution and acute mortality: involvement of ultrafine particles? Inhal Toxicol 7:111–124. https://doi.org/10.3109/08958379509014275

Okubo T, Hosaka M, Nakae D (2015) In vitro effects induced by diesel exhaust at an air–liquid interface in a human lung alveolar carcinoma cell line A549. Exp Toxicol Pathol 67:383–388. https://doi.org/10.1016/j.etp.2015.03.004

Olsson AC et al (2011) Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. Am J Respir Crit Care Med 183:941–948. https://doi.org/10.1164/rccm.201006-0940OC

OSHA, Occupational Safety and Health Administration (2013) HAZARD ALERT – diesel exhaust/diesel particulate matter obtained from https://www.osha.gov/dts/hazardalerts/diesel_exhaust_hazard_alert.html Accessed 12 June 2020

Pawlak EA et al (2016) Diesel exposure suppresses natural killer cell function and resolution of eosinophil inflammation: a randomized controlled trial of exposure in allergic rhinitics. Part Fibre Toxicol 13:24. https://doi.org/10.1186/s12989-016-0135-7

Peretz A et al (2007) Diesel exhaust inhalation and assessment of peripheral blood mononuclear cell gene transcription effects: an exploratory study of healthy human volunteers. Inhal Toxicol 19:1107–1119. https://doi.org/10.1080/08958370701665384

Peretz A et al (2008a) Effects of diesel exhaust inhalation on heart rate variability in human volunteers. Environ Res 107:178–184. https://doi.org/10.1016/j.envres.2008.01.012

Peretz A et al (2008b) Diesel exhaust inhalation elicits acute vasoconstriction in vivo. Environ Health Perspect 116:937–942. https://doi.org/10.1289/ehp.11027

Peters S, de Klerk N, Reid A, Fritschi L, Musk A, Vermeulen R (2017) Estimation of quantitative levels of diesel exhaust exposure and the health impact in the contemporary Australian mining industry. Occup Environ Med 74:282–289. https://doi.org/10.1136/oemed-2016-103808

Prokopowicz A, Zaciera M, Sobczak A, Bielaczyc P, Woodburn J (2015) The effects of neat biodiesel and biodiesel and HVO blends in diesel fuel on exhaust emissions from a light duty vehicle with a diesel engine. Environ Sci Technol 49:7473–7482. https://doi.org/10.1021/acs.est.5b00648

PubChem. "Naphthalene." U.S. National Library of Medicine obtained from: https://pubchem.ncbi.nlm.nih.gov/compound/Naphthalene Accessed 12 Sept 2019

Ramachandran G, Paulsen D, Watts W, Kittelson D (2005) Mass, surface area and number metrics in diesel occupational exposure assessment. J Environ Monit 7:728–735. https://doi.org/10.1039/B503854E

Rider CF, Yamamoto M, Günther OP, Hirota JA, Singh A, Tebbutt SJ, Carlsten C (2016) Controlled diesel exhaust and allergen coexposure modulates microRNA and gene expression in humans: effects on inflammatory lung markers. J Allergy Clin Immunol 138:1690–1700. https://doi.org/10.1016/j.jaci.2016.02.038

Riley EA et al (2018) Evaluation of 1-Nitropyrene as a surrogate measure for diesel exhaust. Ann Work Expo Health 62:339–350. https://doi.org/10.1093/annweh/wxx111

Ris C (2007) U.S. EPA health assessment for diesel engine exhaust: a review. Inhal Toxicol 19:229–239. https://doi.org/10.1080/08958370701497960

Rynning I et al (2019) Bulky DNA adducts, microRNA profiles, and lipid biomarkers in Norwegian tunnel finishing workers occupationally exposed to diesel exhaust. Occup Environ Med 76:10–16. https://doi.org/10.1136/oemed-2018-105445

Seaton A, Godden D, MacNee W, Donaldson K (1995) Particulate air pollution and acute health effects. Lancet 345:176–178. https://doi.org/10.1016/S0140-6736(95)90173-6

Silverman DT 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. https://doi.org/10.1093/jnci/djs034

Steiner S et al (2013) Reduction in (pro-)inflammatory responses of lung cells exposed in vitro to diesel exhaust treated with a non-catalyzed diesel particle filter. Atmos Environ 81:117–124. https://doi.org/10.1016/j.atmosenv.2013.08.029

Steiner S, Bisig C, Petri-Fink A, Rothen-Rutishauser B (2016) Diesel exhaust: current knowledge of adverse effects and underlying cellular mechanisms. Arch Toxicol 90:1541–1553. https://doi.org/10.1007/s00204-016-1736-5

Stevens T, Krantz QT, Linak WP, Hester S, Gilmour MI (2008) Increased transcription of immune and metabolic pathways in Naïve and allergic mice exposed to diesel exhaust. Toxicol Sci 102:359–370. https://doi.org/10.1093/toxsci/kfn006

Tanaka M et al (2013a) Effects of exposure to nanoparticle-rich or -depleted diesel exhaust on allergic pathophysiology in the murine lung. J Toxicol Sci 38:35–48. https://doi.org/10.2131/jts.38.35

Tanaka M, Takano H, Fujitani Y, Hirano S, Ichinose T, Shimada A, Inoue K-I (2013b) Effects of exposure to nanoparticle-rich diesel exhaust on 8-OHdG synthesis in the mouse asthmatic lung. Exp Ther Med 6:703–706. https://doi.org/10.3892/etm.2013.1198

Taxell P, Santonen T (2017) Diesel engine exhaust: basis for occupational exposure limit value. Toxicol Sci 158:243–251. https://doi.org/10.1093/toxsci/kfx110

Tong H et al (2014) Cardiovascular effects caused by increasing concentrations of diesel exhaust in middle-aged healthy GSTM1 null human volunteers. Inhal Toxicol 26:319–326. https://doi.org/10.3109/08958378.2014.889257

Tsukue N, Kato A, Ito T, Sugiyama G, Nakajima T (2010) Acute effects of diesel emission from the urea selective catalytic reduction engine system on male rats. Inhal Toxicol 22:309–320. https://doi.org/10.3109/08958370903307652

US EPA, US Environmental Protection Agency (2002) Health assessment document for diesel engine exhaust. Washington, DC

Valand R et al (2018) Gene expression changes in rat brain regions after 7- and 28 days inhalation exposure to exhaust emissions from 1st and 2nd generation biodiesel fuels - the FuelHealth project. Inhal Toxicol 30:299–312. https://doi.org/10.1080/08958378.2018.1520370

Vermeulen R, Silverman DT, Garshick E, Vlaanderen J, Portengen L, 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. https://doi.org/10.1289/ehp.1306880

Vieira JL, Guimaraes GV, de Andre PA, Cruz FD, Saldiva PHN, Bocchi EA (2016) Respiratory filter reduces the cardiovascular effects associated with diesel exhaust exposure: a randomized, prospective, double-blind, controlled study of heart failure: the FILTER-HF trial. JACC Heart Fail 4:55–64. https://doi.org/10.1016/j.jchf.2015.07.018

Wang H et al (2017) Local and systemic inflammation may mediate diesel engine exhaust–induced Lung function impairment in a Chinese occupational cohort. Toxicol Sci 162:372–382. https://doi.org/10.1093/toxsci/kfx259

Wierzbicka A 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. https://doi.org/10.1016/j.atmosenv.2013.11.025

Win-Shwe T-T, Yamamoto S, Fujitani Y, Hirano S, 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. https://doi.org/10.1016/j.neuro.2008.09.007

Win-Shwe T-T, Fujimaki H, Fujitani Y, Hirano S (2012) Novel object recognition ability in female mice following exposure to nanoparticle-rich diesel exhaust. Toxicol Appl Pharmacol 262:355–362. https://doi.org/10.1016/j.taap.2012.05.015

Yamagishi N et al (2012) Effect of nanoparticle-rich diesel exhaust on testicular and hippocampus steroidogenesis in male rats. Inhal Toxicol 24:459–467. https://doi.org/10.3109/08958378.2012.688225

Yamamoto M, Singh A, Sava F, Pui M, Tebbutt SJ, Carlsten C (2013) MicroRNA expression in response to controlled exposure to diesel exhaust: attenuation by the antioxidant N-Acetylcysteine in a randomized crossover study. Environ Health Perspect 121:670–675. https://doi.org/10.1289/ehp.1205963

Yoza B, Matsumoto M, Matsunaga T (2002) DNA extraction using modified bacterial magnetic particles in the presence of amino silane compound. J Biotechnol 94:217–224. https://doi.org/10.1016/S0168-1656(01)00427-8

Zarcone MC, Duistermaat E, Schadewijk AV, Jedynska A, Hiemstra PS, Kooter IM (2016) Cellular response of mucociliary differentiated primary bronchial epithelial cells to diesel exhaust. Am J Phys Lung Cell Mol Phys 311:L111–L123. https://doi.org/10.1152/ajplung.00064.2016

Zarcone MC, van Schadewijk A, Duistermaat E, Hiemstra PS, Kooter IM (2017) Diesel exhaust alters the response of cultured primary bronchial epithelial cells from patients with chronic obstructive pulmonary disease (COPD) to non-typeable Haemophilus influenzae. Respir Res 18:27–27. https://doi.org/10.1186/s12931-017-0510-4

Zarcone MC et al (2018) Effect of diesel exhaust generated by a city bus engine on stress responses and innate immunity in primary bronchial epithelial cell cultures. Toxicol In Vitro 48:221–231. https://doi.org/10.1016/j.tiv.2018.01.024

Zhang JJ et al (2009) Health effects of real-world exposure to diesel exhaust in persons with asthma. Res Rep Health Eff Inst 184:5–109; discussion 111-123

Zhang X et al (2015) Increased micronucleus, nucleoplasmic bridge, and nuclear bud frequencies in the peripheral blood lymphocytes of diesel engine exhaust-exposed workers. Toxicol Sci 143:408–417. https://doi.org/10.1093/toxsci/kfu239

Zhang X, Hirota JA, Yang C, Carlsten C (2016a) Effect of GST variants on lung function following diesel exhaust and allergen co-exposure in a controlled human crossover study. Free Radic Biol Med 96:385–391. https://doi.org/10.1016/j.freeradbiomed.2016.04.202

Zhang X et al (2016b) Associations between DNA methylation in DNA damage response-related genes and cytokinesis-block micronucleus cytome index in diesel engine exhaust-exposed workers. Arch Toxicol 90:1997–2008. https://doi.org/10.1007/s00204-015-1598-2

Zhu N et al (2012) Environmental nitrogen dioxide (NO_2) exposure influences development and progression of ischemic stroke. Toxicol Lett 214:120–130. https://doi.org/10.1016/j.toxlet.2012.08.021