Literature searches commissioned by Transport for London

1. THE COMEAP Secretariat, with assistance from PHE library services, carried out an initial scoping search to gain an overview of the extent, range and nature of the research literature on the health effects of particulate matter (PM) in underground transport systems. Search terms were developed and tested by qualified PHE librarians in one database (MEDLINE). Information on the search strategy applied is appended as Appendix A.

2. The results of the scoping exercise were discussed at a COMEAP TfL sub-group meeting held on 28 July 2017. The preliminary search revealed a lack of studies assessing the potential health impacts of subway particles. After discussions, the sub-group agreed areas where further searching of the literature were needed to address the questions set out in the terms of reference. The literature search needs were structured around key areas/questions posed by the sub-group.

3. Transport for London (TfL) commissioned Professor Mark Nieuwenhuijsen (ISGlobal, Barcelona) to design and run search strategies across multiple online databases to identify all relevant published and unpublished (grey literature) studies.

4. This paper prepared by Professor Nieuwenhuijsen briefly outlines the search strategies used to identify relevant studies and presents and discusses the results from the literature reviewed. The paper is organised around certain key themes.

5. Note: This is a draft working paper for discussion. It does not reflect the final view of the Committee and should not be cited.

COMEAP Secretariat
June 2018
COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

Literature searches commissioned by Transport for London

1 Evidence on gaseous pollutants in underground transit systems

Literature search

A literature search using the following conditions was undertaken:

The databases searched were:

- EMBASE
- Google Scholar

The search was limited to the following dates: 1 Jan 1980-1 Nov 2017

And the following search string was used

((underground OR subway OR metro) AND (nitrogen dioxide OR Ozone OR Volatile organic compounds))

These searches were supplemented by searches of grey literature resources (eg EU-Life funded project IMPROVE) and hand searching of the reference list of a recent review by Xu and Hao (2017).

Brief summary statements on key studies are presented below. The length and detail of information depends on its relevance to the review question.

Key study summaries

Chang et al (1999) compared exposure to traffic-related pollutants (carbon monoxide (CO), nitric oxides (NOx), total hydro carbon (THC) and ozone (O3)) for six major public commuting modes in Hong Kong. Air pollutant concentrations inside the metro were found to be similar to the other commuting modes (bus, light bus, railway, tram and ferry). The same group also examined commuter's exposure to volatile organic compounds (VOCs) for eight public transportation modes (Chan et al., 2002a). The VOCs concentrations (3.0–3.8 μg m⁻³) inside the metro were ranked second highest after roadway transport cabins (Lau and Chan, 2003). They did, however note that the VOCs exposure levels of metro commuters in Hong Kong were lower than those in most overseas cities.

Li et al. (2006) and Li et al. (2007) measured the concentrations of carbon dioxide (CO₂), CO, total VOC (TVOC), and individual VOCs (benzene, toluene and xylene) in Beijing metro transit system. Only CO showed significant seasonal variations (greater in winter than in summer). The in-train concentrations of VOC species were mainly influenced by the ambient pollutant concentrations; while the in-train concentration of CO₂ was mainly influenced by the number of passengers. Also,
carbonyl compounds were investigated for taxi, bus and metro in Beijing. Metros run on electricity without exhaust had the lowest levels with total concentrations of 98.5 ± 26.3 μg m⁻³ (Pang and Mu, 2007).

A few studies measured VOCs concentrations inside the metro system in Shanghai. The exposure levels of in-train VOCs (benzene, toluene, ethylbenzene, xylene, styrene, formaldehyde, acetaldehyde, acetone and acrolein) were strongly dependent on service time of metro trains, passenger numbers and driving conditions (Gong et al., 2017). The total carbonyl concentrations of in-train were about 1.4–2.5 times lower than in stations. Most carbonyls concentrations were much higher in the morning rush hour than at other times (Feng et al., 2010).

Chan et al. (2002b) and Chan et al. (2003) examined commuter exposure to CO, and VOCs in various public transport environments (metro, bus and taxi) in Guangzhou and found that the exposure levels in metro were noticeably lower than those in the roadway transports.

A comprehensive measurement campaign was conducted to measure the metro indoor CO, CO₂, formaldehyde (HCHO), TVOCs, O₃ in Taipei. The concentrations of CO, CO₂ and HCHO were under the limits in the standards. However, TVOCs exceeded the stipulated standards. In Seoul VOCs were investigated and found below the limit in national standard (Lee et al., 2011).

In Boston, the concentrations of six gasoline related VOCs: benzene, toluene, ethylbenzene, m-/p-xylene, o-xylene and formaldehyde in four different commuting modes (driving, metro, walking, and biking) were compared. The VOCs concentration in metro system was relatively low.

In Mexico City exposure to CO and benzene, was measured on different routes and transport modes in Mexico City. The concentrations of all pollutants were observed lower in metro than other transportation modes at all the time (Gómez-Perales et al., 2004). The commuters’ VOCs exposure levels were also investigated in Mexico City. Benzene, toluene, ethylbenzene, m/p-xylene, and formaldehyde were measured in various transport modes: car, microbus, bus, and metro. The results showed that the average concentrations of all chemicals inside cars and microbuses were statistically higher than in metro trains (Shiohara et al., 2005b).

A high resolution air quality monitoring campaign (particulate matter (PM), CO₂ and CO) was conducted on differently designed station platforms in the Barcelona metro system. Different sized-fractioned PM concentrations varied significantly but CO concentrations were found very low (< 1 ppm) and CO₂ averages range from 371 to 569 ppm (Querol et al., 2012).

In Berlin, a comparison between metro and car exposures showed significantly higher concentrations of PAHs in the metro train, which was explained by relatively high concentrations of fluoranthene and pyrene in the subway (Fromme et al., 1998).

In Athens, TVOCs, were monitored in the metro trains (Assimakopoulos et al., 2013). Highest TVOC concentrations were observed during the morning rush hours (7:00-
The TVOC concentration ranged from 0.02 to 0.60 mg/m$^3$ in the summer period and 0.01 to 2.2 mg/m$^3$ in the winter period.

In Egypt, metro commuters recorded the lowest pollutant levels for all VOC pollutants comparing to other travel mode groups: car, bus, bicycle and walking (Chertok et al., 2004; Knibbs and Dear, 2010).

**Conclusions**

A few studies have measured gaseous pollutants (CO$_2$, O$_3$, VOCs) in metros, mostly in Asia. We considered these studies to be of sufficient quality. Levels tend to be similar or lower than outdoor levels and do not warrant concerns for health. There are no studies in the London underground but we would assume that concentrations would be similar to those of other cities around the world.

2 Evidence on health effects of exposure to underground air pollution on the general public (travelling public or volunteers)

**Literature search**

A literature search using the following conditions was undertaken:  
The databases searched were:  
EMBASE  
Google Scholar

The search was limited to the following dates: 1 Jan 1980-1 Nov 2017

And the following search string was used

$$((\text{underground OR subway OR metro}) \text{ AND (particulates OR particles OR particulate matter}) \text{ AND (health or respirat* OR cardiovascular OR cancer}))$$

These searches were supplemented by the initial scoping search (Annex A), searches of grey literature resources (eg EU-Life funded project IMPROVE) and hand searching of the reference list of a recent review by Xu and Hao (2017).

Brief summary statements on key studies are presented below. The length and detail of information depends on its relevance to the review question.

**Key study summaries**

Klepczynska Nystrom et al (2010) exposed 20 healthy volunteers (mean age of 27 years) to a subway (Odenplan station, Stockholm) in Stockholm and a controlled environment for 2 h, followed by measurements of lung function and the inflammatory response in the lower airways (bronchoscopy) and in the peripheral blood. Subway exposures were performed during afternoon rush hour (16:00-18:00 h; local time). No cellular response was found in the airways after exposure to the subway environment. In the blood, they found a statistically significant increases in fibrinogen and regulatory T-cells expressing CD4/CD25/FOXP3. Although no
cellular response was detected, the findings indicate a biological response to the subway environment.

In a follow up study, Klepczynska-Nystrom, et al (2012) exposed 16 mild asthmatics (mean age 26 years) to a subway (Odenplan, Stockholm) and controlled environment for 2 h while being monitored by measurements of lung function, and inflammatory response in the lower airways evaluated by bronchoscopy and in peripheral blood. Subway exposures were performed during afternoon rush hour (16:00-18:00 h; local time). An attempt to standardize the exposures was done, by letting the volunteer’s alternate 15 min intervals of moderate exercise on a bicycle ergometer with 15 min of rest. They found a statistically significant increased frequency of CD4 cells expressing T-cell activation marker CD25 in bronchoalveolar lavage fluid, but no significant increase of regulatory T-cells in blood as was found in previous study of healthy volunteers (Klepczynska Nystrom et al 2010). The study shows that airway inflammatory responses after exposure in subway environment differ between asthmatic and healthy humans.

Lundstrom, et al (2011) investigated responses of the respiratory system to Stockholm subway air in asthmatics and healthy individuals (from the studies above). 64 eicosanoids and other oxylipins were quantified in the distal lung to provide a measure of shifts in lipid mediators in association with exposure to subway air relative to ambient air. They found that asthmatics and healthy individuals exhibited divergent oxylipin profiles following exposure to ambient and subway air. Significant changes were observed in 8 metabolites of linoleic- and alpha-linolenic acid synthesized via the 15-lipoxygenase pathway, and of the cyclooxygenase product prostaglandin E(2) (PGE(2)). Oxylipin levels were increased in healthy individuals following exposure to subway air, whereas asthmatics evidenced decreases or no change. Several of the altered oxylipins have known or suspected bronchoprotective or anti-inflammatory effects, suggesting a possible reduced anti-inflammatory response in asthmatics following exposure to subway air.

Liu et al (2015) recruited 120 young, healthy subjects (mean age 21.3 year) in Taipei, Taiwan using different commuting routes including an electrically powered subway, a gas-powered bus, a gasoline-powered car, and walking. They obtained three repeated measurements of heart rate variability (HRV) indices (standard deviation of NN intervals (SDNN) and the square root of the mean of the sum of the squares of differences between adjacent NN intervals (r-MSSD)), PM with an aerodynamic diameter <= 2.5 mum (PM2.5), temperature, humidity and noise level were conducted for each subject during 1-h morning commutes (0900-1000 h) in four different commuting modes. Small significant decreases in SDNN (~1.7 (-3.2, -0.2)), but not for r-MSSD (~0.9 (-2.4, 0.6)) were observed among the subjects using the subway. However, the associations between PM exposure and negative health outcomes were greater for the other modes of transportation (car and walking).

Conclusions

In conclusion, four studies have been conducted, mainly in the Stockholm (3 out of the 4) subway using healthy and/or asthmatic volunteers. Most studies have a small number of subjects, and their statistical power is limited for this reason. Although evidence is limited, available studies have reported some minor biological
responses suggesting a mild systemic immune system activation and inflammation during these short-term exposures. The clinical importance of this biochemical observation is unclear. It is also unclear whether exposures have negative long-term health effects. The composition and sources of PM_{2.5} in the Stockholm underground and London Underground are similar. However, concentrations of PM found in the Stockholm underground tend to be lower, particularly in the deep lines, compared to those found in London Underground. At present, it is unclear how these higher concentrations may affect health risks.

3 Evidence on health effects of occupational exposure to underground air pollution

Literature search

A literature search using the following conditions was undertaken:
The databases searched were:
  EMBASE
  Google Scholar

The search was limited to the following dates: 1 Jan 1980-1 Nov 2017

And the following search string was used

((underground OR subway OR metro) AND (particulates OR particles OR particulate matter) AND (health or respirat* OR cardiovascular OR cancer))

These searches were supplemented by the initial scoping search (Annex A), searches of grey literature resources (eg EU-Life funded project IMPROVE) and hand searching of the reference list of a recent review by Xu and Hao (2017).

Brief summary statements on key studies are presented below. The length and detail of information depends on its relevance to the review question.

Key study summaries

Bigert et al (2007) investigated whether there is an increased incidence of myocardial infarction (MI) among subway drivers in Stockholm. Data from a population-based case-control study of men aged 40-69 in Stockholm County in 1976-1996 were used. The study included all first events of MI in registers of hospital discharges and deaths. The controls were selected randomly from the general population. National censuses were used for information on occupation. Altogether, 22 311 cases and 131 496 controls were included. Among these, 54 cases and 250 controls had worked as subway drivers. The relative risk of MI among subway drivers was not increased. It was 0.92 [95% confidence interval (95% CI) 0.68-1.25] when the subway drivers were compared with other manual workers and 1.06 (95% CI 0.78-1.43) when the subway drivers were compared with all other gainfully employed men. Subgroup analyses indicated no influence on the risk of MI from the duration of employment, latency time, or time since employment.
stopped. Subway drivers in Stockholm did not have a higher incidence of MI than other employed persons.

Gustavsson et al (2008) formed a cohort comprised of all men in Stockholm County who were gainfully employed in 1970. They were followed for cancer incidence until 1989. Lung cancer cases were identified from the national cancer register. Subway drivers were identified from the census in 1970. The reference cohort comprised all transport and communication workers in Stockholm. They found nine cases of lung cancer among the subway drivers, giving a standardised incidence ratio (SIR) of 0.82 (95% CI 0.38-1.56). The lung cancer incidence was not increased among the subway drivers.

Bigert et al (2008) investigated risk markers for cardiovascular disease (CVD) in employees exposed to particles in the Stockholm underground system. 79 non-smoking workers (54 men and 25 women) aged 25-50 years were investigated. Three exposure groups were delineated: 29 platform workers with high exposure to particles, 29 train drivers with medium exposure and 21 ticket sellers with low exposure (control group). A baseline blood sample was taken after 2 non-working days, and a second sample after 2 working days, for analysis of levels of plasminogen activator inhibitor-1 (PAI-1), high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), fibrinogen, von Willebrand factor (vWF) and factor VII (FVII). The study investigated changes in plasma concentrations between sample 1 and sample 2, and differences in average concentrations between the groups: No changes between sample 1 and 2 were found that could be attributed to particle exposure. However, the highly exposed platform workers were found to have higher plasma concentrations of PAI-1 and hs-CRP than the ticket sellers and train drivers. This suggests that particle exposure could have a long-term inflammatory effect. These differences remained for PAI-1 in the comparison between platform workers and ticket sellers after adjusting for body mass index.

Bigert et al (2011) investigated airway inflammation and lung function among particle-exposed subway employees. They recruited 81 non-smoking workers, aged 25-50 years. Three exposure groups were formed according to PM levels obtained during an occupational hygienic investigation: 30 platform workers [average PM\textsubscript{2.5} 63 ug/m\textsuperscript{3} and dust (particles 1–10 mm in size, DataRAM MIE Inc, Billerica, Waltham, MA, USA) 182 ug/m\textsuperscript{3}], 30 subway drivers (19 ug/m\textsuperscript{3} and 33 ug/m\textsuperscript{3}) and 21 ticket sellers (10 ug/m\textsuperscript{3} and 13 ug/m\textsuperscript{3}). They measured the fractional exhaled nitric oxide (FENO) of all workers before and after a workday. They also measured the peak expiratory flow (PEF) and forced expiratory volume in one second (FEV\textsubscript{1}) of platform workers and ticket sellers five times a day over two weeks. There was no significant increase in FENO after work among platform workers, subway drivers or ticket sellers (the means of percentual individual change were -7%, +2% and -4% respectively). The averages of the ratios (exposed to unexposed time) of PEF and FEV\textsubscript{1} were above 1.0 for both ticket sellers (1.016 and 1.002 respectively) and platform workers (1.022 and 1.005). The observations do not indicate any short-term respiratory effects of particle exposure in the subway among the employees, with respect to airway inflammation or lung function.

stress, and DNA damage in blood and urine samples. Workers wore a personal air sampler for one to three work shifts with blood and urine samples collected at the end of the final shift. The subway workers' mean time-weighted PM$_{2.5}$ exposure was 52 ug/m$^3$ with a median of 27 ug/m$^3$, and a range of 6-469 ug/m$^3$. The observed concentrations of PM$_{2.5}$, iron (Fe), manganese (Mn), and chromium (Cr) fell well below occupational standards. Biomarker concentrations among the 39 subway workers were compared with a group of 11 bus drivers, and a group of 25 suburban office workers. Concentrations of DNA-protein crosslinks and Cr in plasma were significantly higher in subway workers than in bus drivers, but no significant difference was observed for these biomarkers between subway workers and office workers. Urinary isoprostane concentrations were significantly correlated with the number of years working in the subway system, and were detected at higher, though not significantly higher, concentrations in subway workers than in bus drivers or office workers. At the group level, there was no consistent pattern of biomarker concentrations among subway workers significantly exceeding those of the bus drivers and office workers. At the individual level, steel dust exposure was not correlated with any of the biomarkers measured.

Mehrdad et al (2015) measured urinary level of 8-hydroxy-deoxyguanosine (8-OHdG) as a marker of oxidative stress 81 workers (tunnel workers and other staff) in the Tehran subway. The mean concentration of urinary 8-OHdG for workers in the tunnel was 58.05 (SD=28.83) ng/mg creatinine and for another staff was 54.16 (SD =26.98) ng/mg creatinine. After adjustment for age, smoking, driving and a second job in a linear regression model, the concentration of 8-OHdG for the exposed group was significantly higher than unexposed group (P=0.038).

Conclusions

In conclusion, there have been a few studies evaluating the health effects of occupational exposure to underground air pollution, mostly in the Stockholm underground. The studies often were of poor to moderate quality because of design, unsuitable comparison groups and/or small numbers. In general there were no increased risks for the outcomes studied for underground workers. As noted above, exposure levels to particulate exposure in the Stockholm underground tend to be lower than in the London underground, particularly the deep lines. It is unclear how the higher concentrations found in the London Underground may affect the health risks of workers.

4 Evidence on the toxicity of underground air pollution from experimental (laboratory) studies (in vivo/in vitro)

Literature search

A literature search using the following conditions was undertaken: The databases searched were:
- EMBASE
- Google Scholar

The search was limited to the following dates: 1 Jan 1980-1 Nov 2017
And the following search string was used

((underground OR subway OR metro) AND (particulates OR particles OR particulate matter) AND (in vitro OR in vivo OR experiment*))

These searches were supplemented by the initial scoping search (Annex A), searches of grey literature resources (eg EU-Lifefunded project IMPROVE) and hand searching of the reference list of a recent review by Xu and Hao (2017).

Brief summary statements on key studies are presented below. The length and detail of information depends on its relevance to the review question.

**Key study summaries**

A number of experimental (laboratory) studies (*in vivo or in vitro*) on the toxicity of underground air pollution/PM have been conducted. Most of the studies were conducted with particulate matter from the Stockholm underground, but also from underground systems including London Underground.

Seaton et al (2005) assessed hazards associated with exposure to dust in the London Underground railway. Concentrations of dust, as mass (PM$_{2.5}$) and particle number, were measured at different underground stations and in train cabs; its size and composition were analysed; likely maximal exposures of staff and passengers were estimated; and *in vitro* toxicological testing of sample dusts in comparison with other dusts was performed. Concentrations on station platforms were 270-480 µg/m$^3$ PM$_{2.5}$ and 14,000-29,000 particles/cm$^3$. Cab concentrations over a shift averaged 130-200 µg/m$^3$ and 17,000-23,000 particles/cm$^3$. The dust comprised by mass approximately 67% iron oxide, 1-2% quartz, and traces of other metals, the residue being volatile matter. The finest particles are drawn underground from the surface while the coarser dust is generated by interaction of brakes, wheels, and rails. Toxicology showed the dust to have cytotoxic and inflammatory potential at high doses, consistent with its composition largely of iron oxide.

Karlsson et al (2005) compared the ability of particles from a subway station and a nearby very busy urban street in Stockholm, respectively, to damage DNA and to induce oxidative stress. Cultured human lung cells (A549) were exposed to particles, DNA damage was analysed using single cell gel electrophoresis (the comet assay), and the ability to induce oxidative stress was measured as 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) formation in lung cell DNA. They found that the subway particles were approximately eight times more genotoxic and four times more likely to cause oxidative stress in the lung cells. When the particles, water extracts from the particles, or particles treated with the metal chelator deferoxamine mesylate were incubated with 2'-deoxyguanosine (dG) and 8-oxodG was analysed, they found that the oxidative capacity of the subway particles was due to redox active solid metals. Furthermore, analysis of the atomic composition showed that the subway particles to a dominating degree (atomic %) consisted of iron, mainly in the form of magnetite (Fe$_3$O$_4$). By using electron microscopy, the interaction between the particles and the lung cells was shown.

Karlsson, et al (2006) investigated and compared the genotoxicity and the ability to induce inflammatory mediators of nine different particle types from wood and pellets
combustion, from tire-road wear and collected from an urban street and a subway station in Stockholm. The comet assay was used to assess genotoxicity after exposure of the human lung cell line A549. Inflammatory effects were measured as induction of IL-6, IL-8 and tumour necrosis factor-alpha (TNF-α) after exposure of human macrophages. They found that all particles tested caused DNA damage and those from the subway caused more damage than the other particles (p < 0.001) likely due to redox-active Fe. In contrast, particles collected from an urban street were most potent to induce inflammatory cytokines. Particles from tire-road wear collected using a road simulator were genotoxic and able to induce cytokines.

Karlsson, et al (2008) investigated and compared the toxicity of subway particles and particles from other sources as well as investigate some mechanisms behind the genotoxicity of subway particles in Stockholm. This was done by comparing the ability of subway particles and particles from a street, pure tire-road wear particles, and particles from wood and diesel combustion to cause mitochondrial depolarisation and to form intracellular reactive oxygen species (ROS). Furthermore, the genotoxicity and ability to cause oxidative stress was compared to Fe₃O₄ particles since this is a main component in subway particles. They found that subway dust was more genotoxic than Fe₃O₄, ferric oxide (Fe₂O₃), copper oxide (CuO), or Cu/zinc (Zn) particles, suggesting that the genotoxicity of subway dust could not be solely attributable to these constituent particles. It was concluded that the subway particles and also street particles and particles from wood and diesel combustion caused mitochondrial depolarisation. The ability to damage the mitochondria is thus not the only explanation for the high genotoxicity of subway particles. Subway particles also formed intracellular ROS. This effect may be part of the explanation as to why subway particles show such high genotoxicity when compared to that of other particles. Genotoxicity could, however, not be explained by the main component, Fe₃O₄, by water-soluble metals, or by intracellular mobilised Fe. The genotoxicity is most likely caused by highly reactive surfaces giving rise to oxidative stress.

Lindbom et al (2006) investigated the inflammatory effect of PM₁₀ generated from the wear of studded tires on two different types of pavement in Stockholm. As comparison, they also investigated PM₁₀ from a traffic-intensive street, a subway station, and diesel exhaust particles (DEP). Human monocyte-derived macrophages, nasal epithelial cells (RPMI 2650), and bronchial epithelial cells (BEAS-2B) were exposed to the different types of particles, and the secretion of IL-6, IL-8, IL-10, and TNF-α into the culture medium was measured. The results show a significant release of cytokines from macrophages after exposure for all types of particles. Exposure of epithelial cells to PM₁₀ resulted in a significant increase of TNF-α secreted from BEAS-2B cells for all types of particles used (DEP was not tested), and the highest levels were induced by subway particles. None of the particle types were able to evoke detectable cytokine release from RPMI 2650 cells.

Lindbom, et al (2007) investigated and compared the ability to induce inflammatory mediators of different traffic-related wear particles collected from an urban street, a subway station, and studded tire-pavement wear in Stockholm. Inflammatory effects were measured as induction of NO, IL-6, TNF-α, arachidonic acid (AA), and lipid peroxidation after exposure of the murine macrophage like cell line RAW 264.7. In addition, the redox potential of the particles was measured in a cell-free system. The
results show that all particles tested induce IL-6, TNF-α, and NO, and those from the urban street were the most potent ones. In contrast, particles collected from a subway station were most potent to induce lipid peroxidation, AA release, and formation of ROS. Particles from studded tire-pavement wear, generated using a road simulator, were able to induce inflammatory cytokines, NO, lipid peroxidation, and ROS formation.

Bachoual, et al (2007) conducted a study to evaluate the biological effects of PM sampled at two sites (RER and Metro) in the Paris subway system. Murine macrophages (RAW 264.7) and C57B1/6 mice, respectively, were exposed to 0.01-10 µg/cm² and 5-100 µg/mouse subway PM or reference materials [carbon black (CB), titanium dioxide (TiO₂), or DEPs]. They analysed cell viability, production of cellular and lung pro-inflammatory cytokines [TNF-α, macrophage inflammatory protein (MIP-2), KC (the murin analog of IL-8), and granulocyte macrophage-stimulating factor (GM-CSF)], and mRNA or protein expression of MMP-2, -9, and -12 and heme oxygenase-1 (HO-1). Deferoxamine and polymixin B were used to evaluate the roles of Fe and endotoxin, respectively. Non-cytotoxic concentrations of subway PM (but not CB, TiO₂, or DEPs) induced a time- and dose-dependent increase in TNF-alpha and MIP-2 production by RAW 264.7 cells, in a manner involving, at least in part, PM Fe content (34% inhibition of TNF-α production 8 h after stimulation of RAW 264.7 cells with 10 µg/cm² RER particles pre-treated with deferoxamine). Similar increased cytokine production was transiently observed in vivo in mice and was accompanied by an increased neutrophil cellularity of bronchoalveolar lavage (84.83 +/- 0.98% of polymorphonuclear neutrophils for RER-treated mice after 24 h vs 7.33 +/- 0.99% for vehicle-treated animals). Subway PM induced an increased expression of MMP-12 and HO-1 both in vitro and in vivo. They concluded that PM from the Paris subway system has transient biological effects.

Jung, et al (2012) evaluated the genotoxic effects of organic extract (OE) of subway PM₁₀ and potential attribution of PAHs to these effects in Seoul. Particles were collected in the subway tunnel at Kil-eum station (Line 4) for one month and then extracted with dichloromethane (DCM). Chinese Hamster Ovary cells (CHO-K1) and human normal bronchial cells (BEAS-2B) were exposed to OE, and micronucleus (MN) and Comet assays were conducted to analyse the genotoxicity. The results showed that OE increased DNA or chromosome damages in both cell lines. In the modified Comet assay and MN assay with free radical scavengers, they confirmed that the genotoxic effect of OE was partially due to the oxidative damage on DNA. The Dichloro-dihydro-fluorescein diacetate (DCFH-DA) assay also indicated that OE induced ROS generation in BEAS-2B cells. PAHs [benzo(a)anthracene, benzo(k)fluoranthene, etc.], the most well-known carcinogens in polluted air, were detected in Kil-eum PM₁₀. Their findings confirmed that OE of subway PM₁₀ has genotoxic effects on normal human lung cells, and oxidative stress could be one of the major mechanisms of these genotoxic effects. In addition, some genotoxic and carcinogenic PAHs were detected in OE by GC/MS/MS, even though PAHs level was not enough to increase CYP1A1 gene. They suggested that additive or synergistic effects by unidentified chemicals as well as PAHs contained in OE of subway PM₁₀ may induce genotoxic effects.
Loxham, et al (2015) exposed monolayer and mucociliary air-liquid interface (ALI) cultures of primary bronchial epithelial cells (PBECs) to size-fractionated European underground mainline railway (not further specified) PM (1.1-11.1 μg/m³) and release of lactate dehydrogenase and IL-8 was assayed. ROS generation was measured, and the mechanism of generation studied using desferrioxamine (DFX) and N-acetylcysteine (NAC). Expression of HO-1 was determined by real time quantitative polymerase chain reaction (RT-qPCR). Particle uptake was studied by transmission electron microscopy. Underground PM increased IL-8 release from PBECs, but this was diminished in mucus-secreting ALI cultures. Fine and ultrafine PM generated a greater level of ROS than coarse PM. ROS generation by ultrafine PM was ameliorated by DFX and NAC, suggesting an Fe-dependent mechanism. Despite the presence of mucus, ALI cultures displayed increased HO-1 expression. Intracellular PM was observed within vesicles, mitochondria, and free in the cytosol. The results indicate that, although the mucous layer appears to confer some protection against underground PM, ALI PBECs nonetheless detect PM and mount an antioxidant response.

Spagnolo, et al (2015) evaluated the airborne concentrations of PM₁₀ and three sub-fractions of PM₂.₅ (1-2.5 μm; 0.5-1 μm; 0.25-0.5 μm) in an underground railway system environment (location not further specified) in proximity to platforms and in underground commercial areas within the system, compared these with the outdoor airborne concentrations. They also evaluated the metal components, the cytotoxic properties of the various fractions of particulate matter (PM) and their capacity to induce oxidative stress. Cytotoxicity and oxidative stress were evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and ROS assessment. The concentrations of both PM₁₀ and PM₂.₅ were similar at the three sampling sites. Fe and other transition metals displayed a greater concentration at the subway platform than at the other two sites. The 2.5-10 μm and 1.2-5 μm fractions of PM from all three sampling sites showed a greater increase in ROS; the intensity of oxidative stress progressively declined as particle diameter diminished. Moreover, ROS concentrations were correlated with the concentrations of some transition metals, namely Mn, Cr, Ti, Fe, Cu, Zn, nickel (Ni) and molybdenum (Mo). All PM fractions displayed lower or similar ROS values between platform level and the outdoor air. In conclusion, the underground railway environment at platform level, although containing higher concentrations of some particularly reactive metallic species, did not display higher cytotoxicity and oxidative stress levels than the outdoor air.

Moreno et al (2017) reported on the oxidative potential (OP) of PM₂.₅ samples collected in the Barcelona subway system in different types of stations. The PM chemical composition of these samples showed typically high concentrations of Fe, total carbon, Ba, Cu, Mn, Zn and Cr sourced from rail tracks, wheels, catenaries, brake pads and pantographs. Two toxicological indicators of oxidative activity, ascorbic acid (AA) oxidation (expressed as OPAA mg¹ or OPAA m³) and glutathione (GSH) oxidation (expressed as OPGSH mg¹ or OPGSH m³), showed low OP for all samples (compared with outdoor air) but considerable variation between stations (0.9e2.4 OPAA mg¹; 0.4e1.9 OPGSH mg¹). Results indicate that subway PM toxicity is not related to variations in PM₂.₅ concentrations produced by ventilation changes, tunnel works, or station design, but may be affected more by the presence of metallic trace elements such as Cu and antimony (Sb) sourced from brakes and
pantographs. The OP assays employed do not reveal toxic effects from the highly ferruginous component present in subway dust.

Conclusions

In conclusion, a number of experimental (laboratory) studies (in vivo or in vitro) on the toxicity of underground air pollution/PM have been conducted. Most of the studies were conducted with PM from the Stockholm underground, but also from undergrounds systems including London Underground. The studies were generally of sufficient quality and suggest that PM from underground systems can productive some inflammation, which may at times be stronger than above ground particulate matter. Also it may cause some DNA damage.

5 Stockholm and London Underground: Comparison of air quality and subway characteristics

Summary

As discussed above, the majority of health studies had been conducted in Stockholm. It was therefore important to recognise key differences in terms of number, size and mass of the PM, as well as subway characteristics, such as ventilation. Table 1 (Appendix B) summarises the available relevant information of the included studies.

Overall, these studies support lower concentrations of PM (based on mass concentration) than in the London Underground, particularly for the deeper lines. However, particle size distribution and chemical composition (primarily Fe) appear to be similar.

6 For the health studies identified, any comparable studies on ambient air pollution

Literature search

A literature search using the following conditions was undertaken:

The databases searched were:

  EMBASE
  Google Scholar

The search was limited to the following dates: 1 Jan 1980-1 Nov 2017

And the following search string was used

((particulate* OR particles OR particulate matter) AND (health or respirat* OR cardiovascular OR cancer) AND (transport mode or RAPTES or underground OR subway OR metro))
These searches were supplemented by the initial scoping search (Annex A), searches of grey literature resources (e.g., EU-Life funded project IMPROVE) and hand searching of the reference list of a recent review by Xu and Hao (2017).

Brief summary statements on key studies are presented below. The length and detail of information depends on its relevance to the review question.

**Key study summaries**

Liu et al (2015) recruited 120 young, healthy subjects in Taipei, Taiwan using different commuting routes including an electrically powered subway, a gas-powered bus, a gasoline-powered car, and walking. They obtained three repeated measurements of HRV indices (SDNN and r-MSSD), PM$_{2.5}$, temperature, humidity and noise level were conducted for each subject during 1 h morning commutes (0900-1000 h) in four different commuting modes. The results showed that decreases in the HRV indices were associated with increased levels of PM$_{2.5}$. Small significant decreases in SDNN ($-1.7 (-3.2, -0.2)$), but not for r-MSSD ($-0.9 (-2.4, 0.6)$) were observed among the subjects using the subway. However, the associations between PM exposure and negative health outcomes were greater for the other modes of transportation (car and walking).

Grass, et al (2010) conducted a study of subway workers comparing personal exposures to steel dust with biomarkers of metal exposure, oxidative stress, and DNA damage in blood and urine samples. Workers wore a personal air sampler one to three work shifts with blood and urine samples collected at the end of the final shift. The subway workers' mean time-weighted PM$_{2.5}$ exposure was 52 µg/m$^3$ with a median of 27 µg/m$^3$, and a range of 6-469 µg/m$^3$. The observed concentrations of PM$_{2.5}$, Fe, Mn, and Cr fell well below occupational standards. Biomarker concentrations among the 39 subway workers were compared with a group of 11 bus drivers, and a group of 25 suburban office workers. Concentrations of DNA-protein crosslinks and chromium in plasma were significantly higher in subway workers than in bus drivers, but no significant difference was observed for these biomarkers between subway workers and office workers. Urinary isoprostane concentrations were significantly correlated with the number of years working in the subway system ($r=0.42, P<0.008$), and were detected at higher, though not significantly higher, concentrations in subway workers than in bus drivers or office workers. At the group level, there was no consistent pattern of biomarker concentrations among subway workers significantly exceeding those of the bus drivers and office workers. At the individual level, steel dust exposure was not correlated with any of the biomarkers measured.

The RAPTES study exposed 31 healthy volunteers to air pollution for 5 hours in 5 different locations, including traffic sites and an underground train station, which may somewhat similar to the London Underground and measured a range of different biological changes and health outcomes including white blood cells (WBCs), acute vascular blood biomarkers, thrombin generation, acute nasal airway inflammation, at 2 time periods (2 and 18 h after exposure) (Strak et al 2012, Steenhof et al 2013, Strak et al 2013, Steenhof et al 2014). They measured PM mass and number concentration, its OP, content of elemental/organic carbon, trace metals, sulphate, nitrate and gaseous pollutants (O$_3$, NOx). The highest levels of particulates were
measured in the underground train station (for example, \( \text{PM}_{2.5} = 140 \) (123–167) \( \mu g/m^3 \), \( \text{PNC} = 29.4 \) (14.6–39.8) \( 10^3/cm^3 \)). In general, the study did not find any consistent effects of the specific pollution exposures. Furthermore, the 5 different locations were in general not analysed separately in terms of health effects or compared to each other. Also there were no specific relations reported for Fe.

Changes in total WBC counts (2 and 18 h post-exposure), number of neutrophils (2 h post-exposure) and monocytes (18 h post-exposure) were positively associated with PM characteristics at the underground site. The increase in neutrophils was larger at the underground site than at the outdoor sites (49 and 31%, respectively). In contrast, 18 h post-exposure, they found a significant decrease of 10% in total number of WBC compared to the pre-exposure measurements. The decrease in cell numbers was smaller at the underground site than at the outdoor sites for all subtypes of WBC.

**Conclusions**

In conclusion, only a few studies have been conducted that compared health effects of underground particulate matter with ambient particulate matter. The quality of the studies varied and no consistent picture appeared of the effects.

**7 Assessing toxicity of other settings in which specific emissions are likely to result in exposure to iron-rich dust, namely the iron and steel industry (eg welders, iron foundry and steel workers)**

**Literature search**

A literature search using the following conditions was undertaken:
The databases searched were:
- EMBASE
- Google Scholar

The search was limited to the following dates: 1 Jan 1980-1 Nov 2017

And the following search string was used

\(((\text{particulate}^* \ OR \text{particles} \ OR \text{particulate matter}) \ AND \ (\text{iron}) \ AND \ (\text{health} \ OR \text{respirat}^* \ OR \text{cardiovascular} \ OR \text{cancer}))\)

These searches were supplemented searches of grey literature resources (eg Air Quality Expert Group (AQEG) Understanding \( \text{PM}_{10} \) in Port Talbot) and hand searching of the reference list of a recent review by Xu and Hao (2017).

Brief summary statements on key studies are presented below. The length and detail of information depends on its relevance to the review question.

**Key study summaries**

There have been a number of studies specific to the Utah Valley. The temporary closure of the steel mill in 1986-1987, the primary source of \( \text{PM}_{10} \) in the area,
provided researchers with the unique opportunity to demonstrate correlations between changes in PM$_{10}$ and health outcomes. The studies specific to the Utah Valley, have been broadly separated into two categories: epidemiological studies and experimental studies. This is followed by a summary of any relevant studies of other mills.

Utah Valley steel mill: epidemiological studies

Pope et al (1992) evaluated the association between daily mortality and respirable particulate pollution (PM$_{10}$) in Utah County from April 1985 through December 1989. Poisson regression analysis was used to regress daily death counts on PM$_{10}$ pollution levels, controlling for variability in the weather. A significant positive association between non accidental mortality and PM$_{10}$ pollution was observed. The strongest association was with 5 day moving average PM$_{10}$ levels, including the concurrent day and the preceding 4 days. An increase in 5 day moving average PM$_{10}$ levels, equal to 100 μg/m$^3$, was associated with an estimated increase in deaths per day equal to 16%. The association with mortality and PM$_{10}$ was largest for respiratory disease deaths, next largest for CV deaths, and smallest for all other deaths. Mean PM$_{10}$ concentrations during the study period equaled 47 μg/m$^3$. The maximum 24 h and 5 day moving average PM$_{10}$ levels equaled 365 and 297 μg/m$^3$, respectively. The actual number of deaths in the area were 3.2% higher when the steel mill was open compared to when it was closed (August 1986 and September 1987). Relatively low levels of SO$_2$, aerosol acidity, and O$_3$ suggested an independent association between mortality and PM$_{10}$. The relative risk of death increased monotonically with PM$_{10}$

Parker et al (2008) compared birth outcomes for Utah mothers within and outside the Utah Valley, before, during, and after the steel mill closure between August 1986 and September 1987. The found that mothers who were pregnant around the time of the closure of the mill were less likely to deliver prematurely than mothers who were pregnant before or after; effects were strongest for exposure during the second trimester. Preterm birth within the Utah Valley did not change during the time of mill closure. No patterns for birth weight were observed.

Utah Valley steel mill: experimental studies

Frampton et al (1999) hypothesized that the reduction in hospital respiratory admissions in the Utah Valley during closure of a local steel mill in 1986–1987 was attributable in part to decreased toxicity of ambient air particles. Sampling filters for PM$_{10}$ were obtained from a Utah Valley monitoring station for the year before (year 1), during (year 2), and after (year 3) the steel mill closure. Aqueous extracts of the filters were analysed for metal content and oxidant production and added to cultures of human respiratory epithelial (BEAS-2B) cells for 2 or 24 h. Year 2 dust contained the lowest concentrations of soluble Fe, Cu, and Zn and showed the least oxidant generation. Only dust from year 3 caused cytotoxicity (by microscopy and lactate dehydrogenase release) at 500 μg/ml. Year 1 and year 3, but not year 2, dust induced expression of IL-6 and -8 in a dose-response fashion. The effects of ambient air particles on human respiratory epithelial cells varied significantly with time and metal concentrations.
Dye et al (2001) obtained total suspended particulate filters originally collected near the steel mill during the winter of 1986 (before closure), 1987 (during closure), and 1988 (after plant reopening). PM subcomponents were water-extracted from these filters and Sprague-Dawley rats were intratracheally instilled with equivalent masses of extract. Data indicated that 24 h later, rats exposed to 1986 or 1988 extracts developed significant pulmonary injury and neutrophilic inflammation. Additionally, 50% of rats exposed to 1986 or 1988 extracts had increased airway responsiveness to acetylcholine, compared to 17 and 25% of rats exposed to saline or the 1987 extract, respectively. By 96 h, these effects were largely resolved except for increases in lung lavage fluid neutrophils and lymphocytes in 1986 extract–exposed rats. Analogous effects were observed with lung histologic assessment. Extract analysis using inductively coupled plasma–mass spectroscopy demonstrated in all three extracts nearly 70% of the mass appeared to be sodium-based salts derived from the glass filter matrix. Interestingly, relative to the 1987 extract, the 1986/1988 extracts contained more sulfate, cationic salts (i.e., Ca, potassium (K), magnesium (Mg)), and certain metals (i.e., Cu, Zn, Fe, Pb, Sr, As, Mn, Ni). Although total metal content was ≤ 1% of the extracts by mass, the greater quantity detected in the 1986 and 1988 extracts suggests metals may be important determinants of the pulmonary toxicity observed.

Gio et al (2001) tested the hypothesis that the biologic effect of PM would reflect findings of epidemiology with a greater injury after exposure to an equal mass of particles from those years in which the mill was in operation. Filters containing PM were collected prior to closure of the steel mill, during the closure, and after its reopening. Aqueous extracts of the filters were prepared. One of three extracts (500 µg) was instilled through the bronchoscope into the lungs of non-smoking volunteers. Twenty-four hours later, the same sub-segment was lavaged. Exposure to aqueous extracts of PM collected before closure and after reopening of the steel mill provoked a greater inflammatory response relative to PM extract acquired during the plant shutdown. Findings suggest that mass may not be the most appropriate metric to use in assessing health effects after PM exposure but rather specific components must be identified and assessed.

Wu et al (2001) investigated intracellular signaling mechanisms for pulmonary responses to Utah Valley PM inhalation. Human primary airway epithelial cells were exposed to aqueous extracts of PM collected from the year before (year 1), during (year 2), and after (year 3) the closure of a local steel mill located in the Utah Valley in this study. Transfection with kinase-deficient extracellular signalregulated kinase (ERK) 1 constructs partially blocked Utah Valley PM-induced IL-8 promoter reporter activity. The mitogen-activated protein kinase/ERK kinase (MEK) activity inhibitor PD-98059 significantly abolished IL-8 released in response to Utah Valley PM, as did the epidermal growth factor (EGF) receptor kinase inhibitor AG-1478. Western blotting showed that Utah Valley PM induced phosphorylation of EGF receptor tyrosine, MEK1/2, and ERK1/2, which could be ablated with AG-1478 or PD-98059. For all findings, the potency of Utah Valley PM collected during year 2 was found to be lower relative to that of year 1 and year 3. These data demonstrate that Utah Valley PM can induce IL-8 expression partially through the activation of the EGF receptor signaling.
Pagan et al (2003) analysed water extracts of PM filters from steel mill operational (UE-86, UE-8/1J and closure (UE-87) periods for their elemental composition. Their relative toxicity was determined by exposing primary rodent airway epithelial cultures to equal masses of extracted material. To elucidate extract subcomponents mediating the effects observed, cells were also exposed to surrogate metal mixtures. Potential interactions between the two predominant metals in the UE-86/88 samples, Zn and Cu, were further investigated. Data indicated that, relative to the UE-87 (plant closed) sample, UE-86/88 samples contained more sulfate, Ca, K, Mg and, although present in much lower amounts, a variety of metals including Zn, Cu, Fe, Pb, Sr, Ni, Mn, and V). Cell exposure to UE-86 and UE-8/1J, but not UE-87, resulted in time- and concentration-dependent epithelial injury based on biochemical and light/electron microscopic changes. Cell injury induced by metal mixtures containing equivalent amounts of Zn +Cu + V was commensurate with that induced by the corresponding extract, although divergent antioxidant responses were observed. Exposure to Zn +Cu resulted in significantly greater epithelial toxicity and stress (c-lun N-terminal protein kinase activation) responses than did exposure to Zn or Cu individually. The parallel epithelial injury induced by the extracts and their surrogate Zn +Cu +V mixtures suggests that these metals are mediating the acute airway epithelial effects observed; however, metal interactions appear to play a critical role in the overall cellular effects induced by the PM-derived extracts.

Other mills

Pavanello et al (2016) analysed the expression of EVmiRNAs by real-time PCR which was correlated with oxidative stress, coagulation and inflammation markers, from healthy steel plant workers (n=55) with a well-characterized exposure to PM and PM-associated metals. In-silico ingenuity pathway analysis (IPA) was performed to identify biological pathways regulated by PM-associated EVmiRNA. They found increased expression in 17 EVmiRNAs is associated with PM and metal exposure (p<0.01). Mir-196b that tops the list, being related to 9 different metals, is fundamental in insulin biosynthesis, however three (miR-302b, miR-200c, miR-30d) out of these 17 EVmiRNAs are in turn also related to disruptions (p<0.01) in inflammatory and coagulation markers. The study’s findings support the hypothesis that adverse CV and metabolic effects stemming from inhalation exposures in particular to PM metallic component may be mediated by EVmiRNAs that target key factors in the inflammation, coagulation and glucose homeostasis pathways.

Cakmak et al (2014) examined the relation between acute changes in CV and respiratory function, and PM$_{2.5}$-associated-metals around a steel mill. Using generalised linear mixed models, daily changes in ambient PM$_{2.5}$-associated metals were compared to daily changes in physiologic measures in 59 healthy subjects who spent 5 days near a steel plant and 5 days on a college campus. Fe levels were 294 µg/m$^3$ higher in the steel mill site compared to the college site. Interquartile increases in Ca, Cd, lead (Pb), strontium (Sr), tin (Sn), vanadium (V) and Zn, but not Fe were associated with statistically significant increases in heart rate of 1-3 beats per minute, increases of 1-3 mmHg in blood pressure and/or lung function decreases of up to 4% for total lung capacity.
Tarantini et al (2013) investigated 63 steel workers exposed to a wide range of PM levels, as a work-related condition with well-characterised pro-thrombotic exposure. They measured personal PM$_{10}$, PM$_1$ (≤1 µm) and air metal components. They determined leukocyte DNA methylation of nitric oxide synthase 3 (NOS3) and endothelin 1 (EDN1) through bisulfite-pyrosequencing and we measured endogenous thrombin potential (ETP) as a global coagulation-activation test after standardised triggers. They found that ETP increased in association with PM$_{10}$ (β=20.0, 95% CI 3.0 to 37.0), PM$_1$ (β=80.8 95% CI 14.9 to 146.7) and Zn (β=51.3, 95% CI 0.01 to 111.1) exposures. NOS3 methylation was negatively associated with PM$_{10}$ (β=-0.2, 95% CI -0.4 to -0.03), PM$_1$ (β=-0.8, 95% CI -1.4 to -0.1), Zn (β=-0.9, 95% CI -1.4 to -0.3) and Fe (β=-0.7, 95% CI -1.4 to -0.01) exposures. Zn exposure was negatively associated with EDN1 (β=-0.3, 95% CI -0.8 to -0.1) methylation. Lower NOS3 (β=-42.3; p<0.001) and EDN1 (β=-14.5; p=0.05) were associated with higher ETP. Statistical mediation analysis formally confirmed NOS3 and EDN1 hypomethylation as intermediate mechanisms for PM-related coagulation effects. The study showed for the first time, that gene hypomethylation contributes to environmentally induced hypercoagulability.

Cantone et al (2011) investigated whether the metal components of PM determined activating histone modifications in 63 steel workers with well-characterised exposure to metal-rich PM. They determined histone 3 lysine 4 dimethylation (H3K4me2) and histone 3 lysine 9 acetylation (H3K9ac) on histones from blood leukocytes. Exposure to inhalable metal components (aluminum (Al), Mn, Ni, Zn, arsenic (As), Pb, Fe) and to total PM was estimated for each study subject. Both H3K4me2 and H3K9ac increased in association with years of employment in the plant (p-trend = 0.04 and 0.006, respectively). H3K4me2 increased in association with air levels of Ni [β = 0.16; 95% CI, 0.03-0.3], As (β = 0.16; 95% CI, 0.02-0.3), and Fe (β = 0.14; 95% CI, 0.01-0.26). H3K9ac showed non-significant positive associations with air levels of Ni (β = 0.24; 95% CI, -0.02 to 0.51), As (β = 0.21; 95% CI, -0.06 to 0.48), and Fe (β = 0.22; 95% CI, -0.03 to 0.47). Cumulative exposures to Ni and As, defined as the product of years of employment by metal air levels, were positively correlated with both H3K4me2 (Ni: β = 0.16; 95% CI, 0.01-0.3; As: β = 0.16; 95% CI, 0.03-0.29) and H3K9ac (Ni: β = 0.27; 95% CI, 0.01-0.54; As: β = 0.28; 95% CI, 0.04-0.51).

Bollati et al (2010) evaluated the effects of exposure to PM and PM metal components on candidate miRNAs (miR-222, miR-21, and miR-146a) related with oxidative stress and inflammatory processes in 63 workers at an electric-furnace steel plant. They measured miR-222, miR-21, and miR-146a expression in blood leukocyte RNA on the first day of a workweek (baseline) and after 3 days of work (post-exposure). Relative expression of miRNAs was measured by real-time PCR. They measured blood oxidative stress (8-hydroxyguanine) and estimated individual exposures to PM$_1$, PM$_{10}$, coarse PM (PM$_{10}$ minus PM$_1$), and PM metal components (Cr, Pb, Cd, As, Ni, Mn) between the baseline and post-exposure measurements. They found that expression of miR-222 and miR-21 (using the 2-DeltaDeltaCT method) was significantly increased in post-exposure samples (miR-222: baseline = 0.68 +/- 3.41, post-exposure = 2.16 +/- 2.25, p = 0.002; miR-21: baseline = 4.10 +/- 3.04, post-exposure = 4.66 +/- 2.63, p = 0.05). In post-exposure samples, miR-222 expression was positively correlated with Pb exposure (β = 0.41, p = 0.02), whereas miR-21 expression was associated with blood 8-hydroxyguanine (β = 0.11, p = 0.03)
but not with individual PM size fractions or metal components. Post-exposure expression of miR-146a was not significantly different from baseline (baseline = 0.61 +/- 2.42, post-exposure = 1.90 +/- 3.94, p = 0.19) but was negatively correlated with exposure to lead (β = -0.51, p = 0.011) and Cd (β = -0.42, p = 0.04).

Lall et al (2011) evaluated the association between source-specific daily PM$_{2.5}$ mass and hospital admissions in a time-series investigation that considered both single-lag and distributed-lag model. Daily PM$_{2.5}$ speciation measurements collected in midtown Manhattan were analysed via positive matrix factorisation source apportionment. Daily and distributed-lag generalised linear models of Medicare respiratory and CV hospital admissions during 2001-2002 considered PM$_{2.5}$ mass and PM$_{2.5}$ from five sources: transported sulfate, residual oil, traffic, steel metal works, and soil. Source-related PM$_{2.5}$ (specifically steel and traffic) was significantly associated with hospital admissions but not with total PM$_{2.5}$ mass. Steel metal works-related PM$_{2.5}$ was associated with respiratory admissions for multiple-lag days, especially during the cleanup efforts at the World Trade Center. Traffic-related PM$_{2.5}$ was consistently associated with same-day CV admissions across disease-specific sub-categories. PM$_{2.5}$ constituents associated with each source (eg, elemental carbon with traffic) were likewise associated with admissions in a consistent manner. Mean effects of distributed-lag models were significantly greater than were maximum single-day effect models for both steel- and traffic-related PM$_{2.5}$.

Carvalho-Oliveira et al (2015) compared the adverse effects of two types of real ambient particles; i.e., total suspended particles from an electrostatic precipitator of a steel mill and fine air particles from an urban ambient particulate matter of 2.5 mm, on mucociliary clearance. They quantified mucociliary function by mucociliary transport, ciliary beating frequency and the amount of acid and neutral mucous in epithelial cells through morphometry of frog palate preparations. The palates were immersed in one of the following solutions: total suspended particles (0.1 mg/mL), PM 2.5 mm 0.1 mg/mL (PM$_{0.1}$) or 3.0 mg/mL (PM$_{3.0}$) and amphibian Ringer's solution (control). Particle chemical compositions were determined by X-ray fluorescence and gas chromatography/mass spectrometry. Exposure to total suspended particles and PM$_{3.0}$ decreased mucociliary transport. Ciliary beating frequency was diminished by total suspended particles at all times during exposure, while PM of 2.5 mm did not elicit changes. PM of 2.5 mm reduced epithelial mucous and epithelium thickness, while total suspended particles behaved similarly to the control group. Total suspended particles exhibited a predominance of Fe and no organic compounds, while the particulate matter 2.5 mm contained predominant amounts of S, Fe, Si and, to a lesser extent, Cu, Ni, V, Zn and organic compounds.

Thomson et al (2015) investigated whether size-fractionated particles collected repeatedly in the vicinity of industrial (steel mills and associated coking operations, wastewater treatment), high traffic, and residential areas display systematic differences in biological potency. PM (PM$_{1}$, PM$_{0.1-0.5}$, PM$_{0.5-2.5}$, PM$_{2.5-10}$, PM$_{>10}$) samples collected at sites within Windsor, Ontario, were screened for biological potency in human A549 lung epithelial and murine J774A.1 macrophage-like cells using cytotoxicity bioassays (cellular ATP, resazurin reduction, lactate dehydrogenase (LDH) release), cytokine production, and transcript profiles. Potency was determined from the slope of each dose-effect relationship. Cytotoxic potency varied across size fractions and within a fraction across sites and sampling periods,
suggesting that particle composition, in addition to size and mass, affected particle toxicity. While ATP and LDH profiles showed some similarity, resazurin reduction (a measure of metabolic activity) exhibited a unique pattern of response, indicating that the cytotoxicity assays were sensitive to distinct particle characteristics. Chemical speciation varied in relation to prevailing winds, consistent with enrichment of source emissions (for example, higher metal and PAH content downwind of the industrial site). Notwithstanding this variability, site-dependent differences in particle toxicity were evident, including greater potency of coarse fractions at the industrial site and of ultrafine particles at the traffic site (Site × Size interactions, p < 0.05). Regression of potency against particle constituents revealed correlations between resazurin reduction, induction of metal-responsive genes, and metal content, which were particularly strong for the coarse fraction, and between cytokine release and endotoxin, suggesting that these factors were important drivers of biological effects that explain, at least in part, the contrasting potencies of particles compared on an equivalent mass basis. In conclusion, the data show that 1) particle potency and composition can exhibit significant temporal variation in relation to source contributions; 2) sources may differentially impact the potency of specific size fractions; and 3) particle constituents, notably metals and endotoxin, may elicit distinct biological responses. Together, the data are consistent with the notion that sources and composition, in addition to size and mass concentration, are relevant to particle toxicity.

Conclusions

In conclusion, a number of environmental and occupational studies of health effects of steel mills have been published. The quality of the studies varies and a number of them appeared to be more exploratory studies. The epidemiological studies show some impact of the Utah Valley steel mill closure on some health endpoints. The toxicological studies suggest that PM-associated metals contribute to the observed toxicity. Similar results have been observed for studies of other steel mills. However, no clear picture has emerged as to which metal is most likely to be particularly relevant to health or if interactions play a role, and some of the studies have limitations which makes comparisons harder. Across the studies reviewed, Fe does not appear to be the main component of the PM-induced toxicity. Based upon these considerations, it seems unlikely that risks to health from exposure to emissions from steel mills are a good guide to predicting risks to workers and the travelling public of exposure to underground dust.

8 Studies comparing particulate air pollution exposure and health risk via different modes of transport

Literature search

A literature search using the initial scoping search (Annex A), searches of grey literature resources (eg EU-Life funded project IMPROVE) and hand searching of the reference list of a recent review by Xu and Hao (2017) was undertaken.
Brief summary statements on key studies are presented below. The length and detail of information depends on its relevance to the review question.

**Key study summaries**

Liu et al (2015) recruited 120 young, healthy subjects in Taipei, Taiwan using different commuting routes including an electrically powered subway, a gas-powered bus, a gasoline-powered car, and walking. They obtained three repeated measurements of HRV indices (SDNN and r-MSSD), PM$_{2.5}$, temperature, humidity and noise level were conducted for each subject during 1 h morning commutes (0900-1000 h; local time) in four different commuting modes. The results showed that decreases in the HRV indices were associated with increased levels of PM$_{2.5}$. Small significant decreases in SDNN ($-1.7 (-3.2, -0.2)$), but not for r-MSSD ($-0.9 (-2.4, 0.6)$) were observed among the subjects using the subway. However, the associations between PM exposure and negative health outcomes were greater for the other modes of transportation (car and walking).

Grass, et al (2010) conducted a study of subway workers comparing personal exposures to steel dust with biomarkers of metal exposure, oxidative stress, and DNA damage in blood and urine samples. Workers wore a personal air sampler for one to three work shifts with blood and urine samples collected at the end of the final shift. The subway workers' mean time-weighted PM$_{2.5}$ exposure was 52 ug/m$^3$ with a median of 27 ug/m$^3$, and a range of 6-469 ug/m$^3$. The observed concentrations of PM$_{2.5}$, Fe, Mn, and Cr fell well below occupational standards. Biomarker concentrations among the 39 subway workers were compared with a group of 11 bus drivers, and a group of 25 suburban office workers. Concentrations of DNA-protein crosslinks and Cr in plasma were significantly higher in subway workers than in bus drivers, but no significant difference was observed for these biomarkers between subway workers and office workers. Urinary isoprostane concentrations were significantly correlated with the number of years working in the subway system, and were detected at higher, though not significantly higher, concentrations in subway workers than in bus drivers or office workers. At the group level, there was no consistent pattern of biomarker concentrations among subway workers significantly exceeding those of the bus drivers and office workers. At the individual level, steel dust exposure was not correlated with any of the biomarkers measured.

Woodcock et al (2014) estimated the health benefits of using the London bike sharing system using a comparative risk assessment approach. They estimated the changes in health status when moving from using car, underground or walking to using the public bike sharing system and included physical activity, air pollution and traffic injuries. All routes by road transport were associated with much lower exposure to PM$_{2.5}$ than those reported on the London underground (based on Seaton et al 2015). In aggregate across all trips, the benefit from the averted exposure to PM$_{2.5}$ in the underground approximately balanced the harms from increased inhalation of pollutants as a result of the higher ventilation rates associated with cycling. Therefore, the impact of cycle hire use on average daily exposure was small. Removing the air pollution component of the model had only a small effect on the overall health impacts—for example, from a change of $-83.2$ disability adjusted life years (DALYs) for men from physical activity alone to $-82.8$ DALYs from physical activity and air pollution.
Conclusions

In conclusion, only a few studies compared particulate air exposure and health risks via different modes of transport. In general levels of particulate exposure in the underground systems tend to be higher than in other transport modes or above ground. The studies do not suggest great differences in health effects.

References


R Carvalho-Oliveira, RC Pires-Neto, JOV Bustillo. Chemical composition modulates the adverse effects of particles on the mucociliary epithelium - Clinics, 2015 - *SciELO Brasil*


COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

Dust in the London Underground, a review of the health effects associated with exposure to dust particles – an update from the sub-group

Literature search strategy applied in the scoping exercise to examine the extent of the research literature

COMEAP Secretariat
May 2018
Search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Search Strategy:

1 underground.tw.
2 "enclosed railway**".tw.
3 subway*.tw.
4 metro.tw.
5 metropolitan.tw.
6 1 or 2 or 3 or 4 or 5
7 exp Transportation/
8 exp Railroads/
9 7 or 8
10 6 and 9
11 exp Air Pollution/
12 exp Air Pollutants/
13 exp Particulate Matter/
14 11 or 12 or 13
15 10 and 14
16 coal.tw.
17 15 not 16
Dust in the London Underground, a review of the health effects associated with exposure to dust particles – an update from the sub-group

Table 1 presents a summary of the average daily mean concentrations of PM$_{2.5}$ for the Stockholm and London Underground subway stations and compares metal concentrations as well as the general characteristics of the underground systems.

COMEAP Secretariat
May 2018
<table>
<thead>
<tr>
<th>Study</th>
<th>Place</th>
<th>Study group</th>
<th>Exposure instruments</th>
<th>Time/location of sampling</th>
<th>PM levels</th>
<th>PM composition</th>
<th>Gaseous pollutants</th>
<th>Control measurements</th>
<th>Characteristics of the system</th>
</tr>
</thead>
<tbody>
<tr>
<td>King’s College London</td>
<td>London</td>
<td>Personal monitoring</td>
<td>Micro-aethalometer (AE33); small sensors (TSI Dusttrak, 2 TSI sidepaks; micro-aethalometer); electrometer particle counter (10-300 nm)</td>
<td>measurement s; Nov 2015;  PNC measurement taken over 5 month period of repeat journeys</td>
<td>Low to up 400 $\mu$g/m$^3$ PM$<em>{2.5}$$^a$; highest Victoria Deeper lines above 100 $\mu$g/m$^3$; PM$</em>{2.5}$ mass in Jubilee line 302 $\mu$g/m$^3$ (18 and 26 $\mu$g/m$^3$ in Hyde Park and roadside respectively); for PNC Jubilee line (15,070 particles/cm$^3$, 77nm) (6,521 particles/cm$^3$, 68 nm for Hyde Park &amp; 26,810 particles/cm$^3$, 54 nm for roadside)</td>
<td>Only characterised for Hampstead using inductively coupled plasma mass spectrometry (PM$_{2.5}$) 47% iron oxide; 11% organic matter; 7% elemental carbon, 9% calcium oxide, 3% aluminum oxide, 2% minor elements, 21% unidentified</td>
<td>Not measured</td>
<td>Not measured</td>
<td>No air conditioning No active ventilation No protective protection for workers Steel wheels</td>
</tr>
<tr>
<td>Seaton et al 2005</td>
<td>London</td>
<td>Personal monitoring</td>
<td>PM$_{2.5}$ using a portable DustTrack light scattering monitor; particle number concentration (PNC) using a P-Trak monitor (0.02-1 $\mu$m);</td>
<td>Approx. 2.5 m above platforms (Hampstead, Holland Park &amp; Oxford circus); measurement began around 7 am &amp;</td>
<td>Particle size distribution similar on each station platform, with a medium diameter around 0.4 $\mu$m; about 80% had diameter less than 1 $\mu$m;</td>
<td>64-71% iron oxide by mass in PM$_{2.5}$ (0.1-0.2% chromium, 0.5-1% manganese, &lt;0.1-0.9% copper ; 1-</td>
<td>Not measured</td>
<td>Not measured</td>
<td>No air conditioning No active ventilation No protective protection for workers Steel wheels</td>
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<tr>
<td>TFL (2017)</td>
<td>London</td>
<td>Personal monitoring</td>
<td>Static air sampling for respirable airborne dust at various platforms (minimum of one sample for each line); personal monitoring for respirable airborne dust exposure undertaken on LU train operators whilst driving, on 4-RAIL Analyst simulating passenger journeys; respirable dust results from 0.04-0.66 mg/m³ (highest values at Victoria &amp; Bakerloo); Train operators: highest respirable dust concentration measured was 0.49 mg/m³ for Bakerloo line.; levels recorded for nickel &amp; manganese concentrations below detection limit of &lt;0.01 mg/filter.</td>
<td>Selected samples (train operators) analysed for crystalline silica content; levels below detection limit of &lt;0.01 mg/filter.</td>
<td>Not measured</td>
<td>static airborne dust samples collected by respirable dust samplers continued until 5 pm, on 3 successive days; personal sampling in drivers cabs also carried out for 3 days on each line</td>
<td>average PM$_{2.5}$ ranged from 270 µg/m³ to 480µg/m³ (PNC 14,000 to 29,000 particles/cm³); concentrations in cabs of trains about half of those measured on platforms, whereas average PNCs similar; average personal exposure of station staff ranged from 75-170 µg/m³ (PNC: 14,000-29,000); 2% quartz in respirable dust samples</td>
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RAIL Analysts undertaking passenger journeys & on station staff conducting gate line duties, platform duties & other station duties

| Train operator & passenger dust exposure monitoring on District, Jubilee, Piccadilly, Victoria, Bakerloo, Central, Northern, Circle & Hammersmith & City; Sampling aimed to include peak hours) for all lines were less than workplace concentration exposure limit of 4 mg/m³ (long term 8 h time weighted average) limit of analytical method, between <0.001 & 0.002 mg/m³; chromium & copper concentrations were all below 0.001 mg/m³; iron & zinc concentrations were between 0.02-0.19 mg/m³

<p>| Stizmann et al 1999 | London | Personal exposure of cyclists (30) versus underground train users (3) | Samples collected using Casella personal samplers fitted with a cyclone head at flow rate of 1.9 l/min | Cyclists monitored for approx. 1.5 h/day for 1 week between Nov 1995 &amp; Feb 1996; underground commuters monitored on way to &amp; from work only in tunnel system (i.e. no walk on road) | PM₂.₅ (µg/m³; mean ± SD)) for 6 samples (A-F): A: cyclist 88.54 ± 6.52 (Note: dry weather, no wind) B: cyclist 16.28 ± 4.72 (Note: wind throughout) C: cyclist 1400 ± 2.34 (Note: strong wind) D: cyclist 16.49 ± 4.07 (Note: strong wind) E: LU commuter 892.84 ± 55.18 F: LU commuter 708.60 ± 43.15 | Main particle fraction in road traffic samples are carbon rich particles (84.8%); Fe was 1.4%; For LU 9.7% carbon rich particles, 53.5% Fe-Si-rich | Particles collected by cyclist: agglomerates, highly porous; particles collected by commuter using LU: angular in shape; number concentrations of particles/cm³ ranged for cyclists from 3 particles/cm³ in early morning (04:00-05:00 h) to 157 particles/cm³ in rush hour; |</p>
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<td>Adams et al 2001</td>
<td>London</td>
<td>Comparing transport modes (cycling, bus, car &amp; LU); 19 volunteers is summer &amp; 18 volunteers in winter</td>
<td>Gravimetric high flow personal sampler (PM$_{2.5}$) Sampling only undertaken on weekdays; 4 set times of day representing am &amp; pm, peak &amp; off-peak periods Geometric mean during summer: Cycle: 30.7 µg/m$^3$ Bus: 33.4 µg/m$^3$ Car: 35.0 µg/m$^3$ Tube: 238.7 µg/m$^3$ Tube (above ground line): 27.9 µg/m$^3$ winter: Cycle: 20.2 µg/m$^3$ Bus: 30.9 µg/m$^3$ Car: 23.7 µg/m$^3$ Tube: 103.4 µg/m$^3$</td>
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<td>Klepczynsk a-Nystrom et al 2010</td>
<td>Stockholm</td>
<td>20 healthy volunteers Harvard impactors (PM$_{10/2.5}$); scanning mobility particle sizer (no. concentration for airborne UF) 16:00-18:00 h; subway station (Odenplan); exposures taken at platform</td>
<td>During a total of 10 subway exposures, the mean ± SD levels of PM$<em>{2.5}$ and PM$</em>{10}$ were 77 ± 10 &amp; 242 ± 40 µg/m$^3$ respectively Mean ± SD content of metals in the PM$<em>{10}$ fraction was 58.6 ± 21.0 % iron, 1.0 ± 0.4 % barium, Mean level of NO and NO$<em>2$ was 58 ± 12 &amp; 24 ± 3 µg/m$^3$ respectively Office environment; 16:00-18:00; for the control exposure, the mean ± SD level of PM$</em>{0.1}$-PM$</em>{10}$ Air conditioning on new trains; ventilation through shafts/pressure equilibrating shafts</td>
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samples collected on LU exhibited a higher loading of coarse mode particles with a more even distribution of all sized particles (Note: cut off 0.2 µm)
particles with an aerodynamic diameter of 14-100 nm); chemiluminescent instrument (NO/NO₂)

| Number concentration of ambient airborne particles <100 nm was 8,283 ± 1,716 particles/ml¹ | 0.8 ± 0.4 % copper & 0.5 ± 0.2 % manganese; content of metals in PM₂.₅ fraction was below limit of detection |

| Mean ± SD content of metals in the PM₁₀ fraction was 49.3 ± 7.3 % iron, 0.7 ± 0.1 % barium & 0.4 ± 0.1 % manganese; copper below limit of detection content of metals in PM₂.₅ fraction was | Mean level of NO and NO₂ was 43 ± 14 & 20 ± 3 µg/m³ respectively |

| (using DataRAM) was 16 ± 4 µg/m³ (subway environment 162 ± 25 µg/m³); number of particles between 20 & 1000 nm (using P-Trak) was 1,007 ± 660 particles/ml¹ (subway 10,549 ± 1,453 particles/ml¹) | Office environment: 16:00-18:00; for the control exposure, the mean ± SD level of PM₀.₁-PM₁₀ (using DataRAM) was 18 ± 4 µg/m³ (subway environment 150 ± 30 µg/m³); number of Air conditioning on new trains; ventilation through shafts/pressure equalizing shafts |

| Klepczynsk a-Nystrom et al 2012 | Stockholm | 16 asthmatics | Harvard impactors (PM₁₀₂.₃); scanning mobility particle sizer (no. concentration for airborne UF particles with an aerodynamic diameter of 10-100 nm); chemiluminescent instrument (NOx) | 16:00-18:00 h; subway station (Odenplan); exposures taken at platform | During a total of 11 subway exposures, the mean ± SD levels of PM₂.₅ and PM₁₀ were 71 ± 13 & 232 ± 51 µg/m³ respectively |

<p>| Number concentration of ambient airborne particles &lt;100 nm was 8,960 ± 660 particles/ml¹ | |</p>
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1. Bigert et al., 2011; Stockholm; 81 employees (non-smoking); Personal sampling (in subset of 44) during two work shifts (each approx. 8 h); PM2.5 (cyclone GK2.05); real time particle measurements (DataRAM) [0.1-10 µm].

2. Bigert et al., 2011; Stockholm; 81 employees (non-smoking); Personal sampling (in subset of 44) during two work shifts (each approx. 8 h); PM2.5 (cyclone GK2.05); real time particle measurements (DataRAM) [0.1-10 µm].

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4. The mean ± SD levels of PM<sub>2.5</sub> were 10 ± 3, 19 ± 3 & 63 ± 12 µg/m<sup>3</sup> for ticket sellers, subway drivers & platform workers respectively. DataRAM (µg.m<sup>3</sup>): 13 ± 3, 33 ± 12 & 182 ± 57 for ticket sellers, subway drivers & platform workers respectively.

5. The mean ± SD levels of PM<sub>2.5</sub> were 10 ± 3, 19 ± 3 & 63 ± 12 µg/m<sup>3</sup> for ticket sellers, subway drivers & platform workers respectively. DataRAM (µg.m<sup>3</sup>): 13 ± 3,

| Stockholm | Compared measurement underground to busy street (Hornsgatan) | PM10 & PM2.5 measured using an automatic TEOM®; CO monitored using a commercial instrument based on absorption of IR light in a cell; same instruments used for measurements at street level | Instruments placed in centre of northbound platform of the underground station ‘Mariatorget’ | During daytime PM$_{10}$ hourly average measurements in underground 469 µg/m$^3$ compared to 98 µg/m$^3$ at street level; During daytime PM$_{2.5}$ hourly average measurement in underground 258µg/m$^3$ compared to 23.1 µg/m$^3$ at street level; lower concentration at weekend opposed to weekday |