Annex C. Human Clinical Studies

Table C-1. Cardiovascular Effects

Reference	Subjects	Particle Characteristics	Exposure	Findings
Barregard et al. (2006)	13 healthy adults; 6 M/ 7 F; 20-56 years old	Wood smoke with fine particulate concentration of 240-280 μg/m^3	Subjects exposed for 4 h to filtered air, followed a week later by a 4 h exposure to wood smoke. Exposures conducted with two 25-min periods of light exercise.	Statistically significant increase in plasma factor VIII 20 h post wood smoke exposure relative to filtered air. The factor VIII/von Willebrand ratio in plasma was increased with wood smoke relative to filtered air at 0, 3, and 20 h post-exposure. Wood smoke exposure increased the urinary excretion of free 8-iso-prostaglandin$_{2\alpha}$ relative to clean air 20 h post-exposure (n = 9).
Beckett et al. (2005)	12 healthy adults; 6 M/6 F; 23-52 years old	Ultrafine (<0.1 μm) and fine (0.1-1.0 μm) zinc oxide; 500 μg/m^3	Subjects exposed via mouthpiece for 2-h during rest to filtered air, ultrafine, and fine zinc oxide in a randomized crossover study design. Exposures were separated by at least 3 weeks.	Exposure to ultrafine and fine zinc oxide did not affect HRV (time and frequency domain parameters) relative to clean air immediately following exposure, or at 3, 6, 11, and 23 h post-exposure. Exposure did not affect blood pressure through 24-h post-exposure. No effects of exposure to either fine or ultrafine zinc oxide observed on factor VII, von Willebrand factor (vWf), tissue plasminogen activator (t-PA), or fibrinogen. No effect of exposure observed on peripheral blood cell counts or levels of pro-inflammatory cytokines.
Brauner et al. (2007)	29 healthy adults; 20 M/9 F; 20-40 years old	Urban traffic particles; avg $PM_{2.5}$ concentration 9.7 μg/m^3, avg $PM_{2.5-10}$ concentration 12.6 μg/m^3	Subjects exposed to urban traffic particles and filtered air for 24-h in a randomized crossover study design. Each exposure included two 90 min periods of light exercise.	An increase in DNA strand breaks and formamidopyrimidine-DNA glycosylase sites in peripheral blood mononuclear cells were observed after 6 and 24-h of exposure to urban particulates. The particle concentration at the 57 nm mode was shown to be the major contributor to these effects.
Brauner et al. (2008)	42 healthy older adults (21 couples); 60-75 years old	Indoor air particles; avg coarse concentration 9.4 μg/m^3; avg fine concentration 12.6 μg/m^3	Exposures consisted of two 48 h periods in the home of each subject with or without the use of a HEPA filter (randomized crossover design). HEPA filters reduced coarse concentration from 9.4 to 4.6 μg/m^3, and fine concentration from 12.6 to 4.7 μg/m^3.	The use of HEPA filters significantly improved microvascular function (p = 0.04) after 48 h. Microvascular function was assessed using a scoring system representing the extent of reactive hyperemia. The reduction in PM concentration through the use of HEPA filters did not significantly affect blood pressure following the 48 h exposures. Lowering PM concentration did not significantly affect inflammatory response markers in peripheral venous blood (IL-6, TNF-α, C-reactive protein, plasma amyloid A).
Carlsten et al. (2007)	13 healthy adults; 11 M/2 F; 20-42 years old	DE; fine PM concentrations 100 and 200 μg/m^3	Subjects exposed for 2-h at rest to filtered air and each of the two DEPs concentrations in a randomized crossover study design. Exposures were separated by at least 2 weeks.	No statistically significant changes in plasminogen activator inhibitor-1 (PAI-1), vWf, D-dimer, or platelet count observed 3, 6, or 22-h following exposure to DE relative to filtered air. Non-statistically significant increases in D-dimer, vWf, and platelet count was observed at 6 h following the start of exposure (4 h post-exposure). No diesel-induced increase in C-reative protein observed in relative to filtered air in peripheral venous blood at 1 or 20 h post-exposure.
Carlsten et al. (2008)	16 adults with metabolic syndrome; 10 M/6 F; 25-48 years old	DE; fine PM concentrations 100 and 200 μg/m^3	Subjects exposed for 2-h at rest to filtered air and each of the two DE particle concentrations in a randomized crossover study design. Exposures were separated by at least 2 weeks.	At 5 h after the end of diesel exposure (fine particulate concentration 200 μg/m^3), the authors observed a significant decrease in vWf in peripheral venous blood. No other changes in thrombotic markers (vWf, D-dimer, PAI-1) were observed at either concentration between 1 and 20 h post-exposure.
Danielsen et al. (2008)	13 healthy adults; 6 M/ 7 F; 20-56 years old	Wood smoke with fine particulate concentration of 240-280 μg/m^3	Subjects exposed for 4 h to filtered air, followed a week later by a 4 h exposure to wood smoke. Exposures conducted with two 25 min periods of light exercise.	Exposure to wood smoke increased the mRNA levels of hOGG1 in PBMCs relative to filtered air 20 h after exposure. DNA strand breaks were shown to decrease in PBMCs 20 h after wood smoke exposure.
Devlin et al. (2003)	10 healthy older adults; 7 M/ 3 F; avg age 66.9 years	Fine CAPs (Chapel Hill, NC); mean concentration 40.5 μg/m^3 (range 21.2-80.3 μg/m^3)	Exposures conducted in an inhalation chamber for 2-h at rest to filtered air and CAPs in a randomized crossover study design.	CAPs exposure resulted in statistically significant reductions (p <0.05) in time domain (PNN50) and frequency domain (HF power) parameters relative to clean air immediately following exposure. These relative decreases were still apparent 24-h after exposure (p <0.08).

Reference	Subjects	Particle Characteristics	Exposure	Findings
Frampton et al. (2006)	16 asthmatic adults (8 M/8 F), 40 healthy adults (20 M/20 F); 18-40 years old	Ultrafine elemetal carbon; 10, 25, and 50 μg/m^3	Study conducted using a randomized crossover design with 2-h exposures. Asthmatics (n = 16) exposed to filtered air and 10 μg/m^3. 12 healthy adults exposed to filtered air and 10 μg/m^3 at rest; 12 healthy adults exposed to filtered air, 10 and 25 μg/m^3 with intermittent exercise; 16 healthy adults exposed to filtered air and 50 μg/m^3 with intermittent exercise. Exposures were conducted via mouthpiece.	No effect of ultrafine particle exposure on leukocyte counts or leukocyte expression of adhesion molecules observed in healthy subjects exposed at rest to 10 μg/m^3. Among healthy adults exposed to ultrafine carbon during exercise, monocyte expression of adhesion molecules CD54 and CD18 decreased relative to filtered air immediately following exposure. An ultrafine particle-induced decrease in PMN expression of CD18 was also observed 0-21-h post-exposure. Expression of CD11b on monocytes and eosinophils was reduced following exposure to ultrafine particles in exercising asthmatics 0-21-h post-exposure. A decrease in total leukocyte count was observed following ultrafine particle exposure in exercising healthy and asthmatic subjects.
Gong et al. (2004a)	13 older adults with COPD (5 M/ 8 F; avg age 68 years); 6 healthy older adults (2 M/4 F; avg age 73 years)	Fine CAPs (Los Angeles); mean concentration 194 μg/m^3 (range 135-229 μg/m^3)	Exposures to CAPs and filtered air (randomized crossover) conducted in an inhalation chamber for 2-h with intermittent light exercise (four 15-min periods). Exposures were separated by at least 2 weeks.	SDNN shown to decrease following CAPs exposure relative to filtered air in healthy older adults (4-22-h post-exposure). No CAPs-induced changes in HRV were observed in older adults with COPD.
Gong et al. (2004b)	12 adult asthmatics (4 M/8 F; avg age 38 years); 4 healthy adults (2 M/2 F; avg age 32 years)	Coarse CAPs (Los Angeles); 80% of mass between 2.5 and 10 μm, 20% of mass <2.5 μm; mean concentration 157 μg/m^3 (range 56-218 μg/m^3)	Exposures to CAPs and filtered air (randomized crossover) conducted in an inhalation chamber for 2-h with intermittent light exercise (four 15-min periods). Exposures were separated by at least 2 weeks.	SDNN shown to decrease following CAPs exposure relative to filtered air in healthy adults (4-22-h post-exposure). Decrease in PNN50 also observed in healthy adults at 4 h post-exposure. No CAPs-induced decreases in HRV demonstrated in asthmatics.
Gong et al. (2008)	14 adult asthmatics (9 M/5 F; age 34 ± 12 years); 17 healthy adults (5 M/12 F; age 24 ± 8 years)	Ultrafine CAPs (Los Angeles); mean concentration 100 μg/m^3 (range 13-277 μg/m^3)	Subjects exposed for 2-h during intermittent exercise (15 min periods) to both CAPs and filtered air in random order, with exposures separated by at least 2 weeks.	Relative to filtered air, exposure to ultrafine CAPs resulted in a transient decrease in LF power 2-h post-exposure. This effect of CAPs on HRV was not influenced by health status.
Larsson et al. (2007)	16 healthy adults; 10 M/6 F; 19-59 years old	Traffic particulates (road tunnel); $PM_{2.5}$: 46-81 μg/m^3; PM_{10}: 130-206 μg/m^3	Exposures were conducted for 2-h with intermittent exercise in a room adjacent to a busy road tunnel. Study used a randomized crossover design with each subject also exposed to normal air (control). Exposures were separated by 3-10 weeks. No exposures to filtered air were conducted.	No change in plasma levels of fibrinogen or PAI-1 observed 14 h post-exposure.
Mills et al. (2005)	30 healthy males; 20-38 years old	DE; particulate concentration 300 μg/m^3	Subjects exposed for 1-h with intermittent exercise (15-min periods) to DE and filtered air in a randomized crossover study design. Exposures were separated by two weeks.	Forearm blood flow increase (induced by bradykinin, acetylcholine, and sodium nitroprusside) was attenuated by DE 2 and 6 h post-exposure. A 6 mmHg increase in diastolic blood pressure (p = 0.08) 2-h following exposure to DE was observed relative to filtered air control. Bradykinin-induced release of t-PA was attenuated by diesel exposure 6 h post-exposure. DE did not affect the release of t-PA 2-h post-exposure. No diesel-induced changes in serum IL-6 or TNF-α observed 6 h post-exposure.
Mills et al. (2007)	20 older adult males with prior myocardial infarction; age 60 ± 1 years	DE; particulate concentration 300 μg/m^3	Subjects exposed for 1-h with intermittent exercise (15-min periods) to DE and filtered air in a randomized crossover study design. Exposures were separated by at least two weeks.	A greater increase in exercise induced ST-segment depression and ischemic burden was observed during exposure to DE than clean air. No diesel-induced effects on vasomotor dysfunction observed 6 h post-exposure. Bradykinin-induced release of t-PA was attenuated by diesel exposure relative to filtered air 6 h post-exposure. Effect of diesel on t-PA release was not evaluated at earlier times post-exposure. No diesel-induced changes in blood leukocyte counts or serum C-reactive protein 6 h post-exposure.
Mills et al. (2008)	12 adult males with coronary heart disease (age 59 ± 2 years); 12 healthy adult males (age 54 ± 2 years)	Fine CAPs (Edinburgh, Scotland, UK); concentration 190 ± 37 μg/m^3	Exposures conducted in an exposure chamber for 2-h with intermittent exercise. Subjects exposed to CAPs and filtered air using a randomized crossover design with exposures separated by at least 2 weeks.	CAPs exposure had no significant effect on vascular function 6-8 h post-exposure (i.e., no change in forearm blood flow as assessed using venous occlusion plethysmography). The authors attributed this lack of response to a low concentration of combustion-derived particles.

Reference	Subjects	Particle Characteristics	Exposure	Findings
Peretz et al. (2007)	5 healthy males; 20-31 years old	DE; fine particulate concentrations of 50, 100, and 200 μg/m^3	Subjects exposed for 2-h at rest to filtered air and each of the three DE particle concentrations in a randomized crossover study design. Exposures were separated by at least 2 weeks.	PBMC expression of 10 genes involved in the inflammatory response were observed to be significantly affected by exposure to DE at the highest concentration tested (8 upregulated, 2 downregulated) 6 h after the start of exposure. The expression of 4 genes (1 upregulated, 3 downregulated) associated with the inflammatory response showed significant changes 22-h after diesel exposure. PBMC expression of 5 genes involved in the oxidative stress pathways showed significant changes at 6 h after the start of diesel exposure at the highest concentration tested (4 upregulated, 1 downregulated). 7 genes involved in the oxidative stress pathways showed significant changes at 22-h following exposure (4 upregulated, 3 downregulated).
Peretz et al. (2008a)	17 adults with metabolic syndrome (11 M/6 F; 20-48 years old); 10 healthy adults (8 M/2 F; 20-42 years old)	DE; fine PM concentrations of 100 and 200 μg/m^3	Subjects exposed for 2-h at rest to both concentrations of DE as well as filtered air in a randomized crossover design. Exposures were separated by at least 2 weeks.	Exposure to 200 μg/m^3 elicited a statistically significant decrease in brachial artery diameter relative to filtered air immediately following exposure. A smaller decrease in brachial artery diameter was also observed following exposure to DE at 100 μg/m^3. Plasma levels of endothelin-1 were observed to increase following DE exposure (200 μg/m^3). DE did not affect endothelium-dependent flow-mediated dilatation. No effect of DE on blood pressure was demonstrated immediately following exposure.
Peretz et al. (2008b)	13 adults with metabolic syndrome (8 M/5 F; 31-48 years old); 3 healthy adults (3 M/0 F; 24-39 years old)	DE; fine PM concentrations of 100 and 200 μg/m^3	Subjects exposed for 2-h at rest to both concentrations of DE as well as filtered air in a randomized crossover design. Exposures were separated by at least 2 weeks.	Exposure to 200 μg/m^3 increased HF power and decreased the LF/HF ratio 1-h post-exposure; however, this effect was not consistent across subjects. No effect of DE was observed at later time points. Subjects with metabolic syndrome did not experience greater changes in HRV than healthy subjects.
Routledge et al. (2006)	20 older adults with coronary artery disease (17 M/3 F; 52-74 years old); 20 healthy older adults (10 M/10 F; 56-75 years old)	Ultrafine carbon (<10-300 nm; mode at 20-30 nm); concentration 50 μg/m^3; SO_2 concentration 200 ppb	Exposures conducted (head dome system) to filtered air, ultrafine carbon, SO_2, and ultrafine carbon + SO_2 for 1-h at rest using a randomized crossover study design.	No PM-induced changes in HRV observed among subjects with coronary artery disease. Among healthy subjects, small increase in HRV (RR, SDNN, rMSSD, and LF power) demonstrated immediately post-carbon exposure. Relative to filtered air control, exposure to ultrafine carbon did not significantly affect blood pressure in healthy adults or adults with coronary artery disease 0-3 h post-exposure. Exposure to ultrafine carbon, either alone or with SO_2, did not affect plasma levels of fibrinogen or D-dimer at 3 or 23 h post-exposure. Exposure to ultrafine carbon did not affect peripheral blood leukocyte count or C-reactive protein levels 3 or 23 h post-exposure.
Samet et al. (2007)	Ultrafine CAPs: (20 healthy adults; 11 M/9 F; 18-35 years old); Coarse CAPs: (14 healthy adults; 8 M/6 F; 18-35 years old)	CAPs (Chapel Hill, NC): Ultrafine (0.049 ± 0.009 μm); concentration 47.0 ± 20.2 μg/m^3; Coarse (3.59 ± 0.58 μm); concentration 89.0 ± 49.5 μg/m^3	Randomized crossover studies of 2-h exposures (chamber) with intermittent exercise to either ultrafine (n = 20) or coarse (n = 14) CAPs using filtered air as control in both studies. Results compared with previous study of controlled exposure to fine CAPs (Chapel Hill, NC) where subjects did not serve as their own controls (Ghio et al., 2000).	Statistically significant decrease in SDNN observed 20 h following exposure to coarse CAPs relative to filtered air. Subjects in the high ultrafine CAPs group experienced a decrease in SDNN based on an analysis of 24-h ambulatory Holter monitoring relative to filtered air. Fine CAPs did not significantly affect HRV. Increased levels of D-dimer observed 18 h following exposure to ultrafine CAPs. No CAPs-induced changes in plasma factor VII, plasminogen, fibrinogen, PAI-1, vWf, or t-PA. No CAPs-induced changes in C-reactive protein levels were observed.
Shah et al. (2008)	16 healthy adults; age 26.9 ± 6.9 years	Ultrafine elemental carbon; concentration 50 μg/m^3	Exposures conducted via mouthpiece for 2-h with intermittent exercise to filtered air and ultrafine carbon in a randomized crossover study design.	Exposure to ultrafine carbon attenuated peak forearm blood flow after ischemia relative to filtered air 3.5 h post-exposure. PM exposure was not observed to affect blood pressure relative to filtered air at times 0-45 h post-exposure.
Tornqvist et al. (2007)	15 healthy adult males; 18-38 years old	DE; particulate concentration 300 μg/m^3	Subjects exposed for 1-h with intermittent exercise (15-min periods) to DE and filtered air in a randomized crossover study design. Exposures were separated by at least two weeks.	DE was observed to significantly attenuate endothelium-dependent vasodilation 24-h post-exposure. Endothelium-independent vasodilation was not affected by diesel exposure. Exposure to DE did not affect blood pressure relative to filtered air 24-h after exposure. DE significantly increased plasma levels of IL-6 and TNF-α 24-h following exposure. Exposure to diesel resulted in an increase in total antioxidant capacity of plasma relative to filtered air 24-h post-exposure.

Reference	Subjects	Particle Characteristics	Exposure	Findings
Urch et al. (2004)	24 healthy adults; 14 M/10 F; age 35 ± 10 years	Fine CAPs (Toronto); 150 μg/m^3 (range 101-257 μg/m^3) with 120 ppb ozone	Exposures conducted through a facemask which covered the subject's nose and mouth. Subjects were exposed to CAPs + ozone and filtered air for 2-h at rest in a randomized crossover study design.	CAPs + ozone exposure resulted in a significant decrease in brachial artery diameter immediately post-exposure (Brook et al., 2002), which was demonstrated to be associated with both the organic and elemental carbon fractions of the CAPs.
Urch et al. (2005)	23 healthy adults; 13 M/10 F; age 32 ± 10 years	Fine CAPs (Toronto); 150 μg/m^3 (range 102-214 μg/m^3) with 120 ppb ozone	Exposures conducted through a facemask which covered the subject's nose and mouth. Subjects were exposed to CAPs + ozone and filtered air for 2-h at rest in a randomized crossover study design.	An increase in diastolic blood pressure of 6 mmHg was observed at the end of CAPs + ozone exposure, which was statistically different from the change in blood pressure experienced during exposure to filtered air (1 mmHg).

Table C-2. Respiratory effects

Reference	Subjects	Particle Characteristics	Exposure	Findings
Alexis et al. (2006)	9 healthy adults; 3 M/6 F; 18-35 years old	Coarse fraction CAPs (Chapel Hill, NC); heat-treated (biologically inactive) and non-heated CAPs; 0.65 mg per subject	Subjects were administered heat-treated $PM_{2.5\ -10}$, non-heated $PM_{2.5\ -10}$, and 0.9% saline (control) via nebulization in a randomized crossover study design. Exposures were separated by at least 1 week.	Both heat-treated and non-heated coarse PM were observed to increase neutrophil counts in induced sputum 2-3 h post-inhalation. Biologically active PM (non-heated) induced an increase expression of macrophage TNF-α mRNA, eotaxin, and immune surface phenotypes on macrophages (mCD14, CD11b/CR3, and HLA-DR).
Barregard et al. (2008)	13 healthy adults; 6 M/ 7 F; 20-56 years old	Wood smoke with fine particulate concentration of 240-280 μg/m^3	Subjects exposed for 4 h to filtered air, followed a week later by a 4 h exposure to wood smoke. Exposures conducted with two 25 min periods of light exercise.	Relative to filtered air, exposure to wood smoke was observed to increase levels of eNO 3f h post-exposure. Serum Clara cell protein increased 20 h after wood smoke exposure. Wood smoke was observed to increase levels of malondialdehyde in breath condensate immediately after as well as 20 h post-exposure.
Bastain et al. (2003)	18 nonsmoking adults with positive allergy skin test to short ragweed; 7 M/11 F; 18-38 years old	DEP; 0.3 mg in 200 μl saline	Subjects underwent nasal provocation challenge (intranasal spray) with allergen and either DEP or placebo (saline) in a randomized crossover study design. Challenges were separated by 30 days. This protocol was then repeated 30 days after the last exposure.	DEP significantly increased allergic responses to short ragweed. Relative to allergen + placebo, allergen + DEP increased allergen specific IgE 4 days following exposure, and increased IL-4 1 day post-exposure. The enhancement of allergic response with DEP was observed to be reproducible within subjects.
Beckett et al. (2005)	12 healthy adults; 6 M/6 F; 23-52 years old	Ultrafine (<0.1 μm) and fine (0.1-1.0 μm) zinc oxide; 500 μg/m^3	Subjects exposed via mouthpiece for 2-h during rest to filtered air, ultrafine, and fine zinc oxide in a randomized crossover study design. Exposures were separated by at least 3 weeks.	No changes observed in neutrophil count in induced sputum. No PM (zinc oxide)-induced changes in respiratory symptoms observed 0-24-h post-exposure.
Behndig et al. (2006)	15 healthy adults; 8 M/7 F;21-27 years old	DE; PM_{10} concentration 100 μg/m^3	Exposures conducted for 2-h with intermittent exercise to both DE and filtered air in a randomized crossover design. Exposures were separated by at least 3 weeks.	Exposure to DE increased neutrophil and mast cell numbers in bronchial mucosa at 18 h post-exposure. Neutrophils, IL-8, and myeloperoxidase observed to increase in bronchial lavage fluid following exposure relative to filtered air. No inflammatory response observed in the alveolar compartment. Exposure to DE increased urate and reduced glutathione bronchoalveolar lavage at 18 h post-exposure.
Bosson et al. (2007)	16 healthy adults; 7 M/9 F; 20-28 years old	DE (PM concentration 300 μg/m^3) followed by exposure to filtered air or 0.2 ppm ozone	Subjects exposed to DE for 1-h followed 5 h later by a 2-h exposure to either filtered air or ozone (0.2 ppm) using a randomized crossover study design. All exposures were conducted with subjects engaged in intermittent exercise.	The percentage of neutrophils and concentration of myeloperoxidase in induced sputum (18 h post-ozone/air exposure) was significantly higher following diesel + ozone than diesel + air.

Reference	Subjects	Particle Characteristics	Exposure	Findings
Bosson et al. (2008)	14 healthy adults; 9 M/5 F; 21-29 years old	DE (PM concentration 300 μg/m^3) or filtered air followed by exposure to 0.2 ppm ozone	Subjects exposed to DE or filtered air for 1-h followed 5 h later by a 2-h exposure to ozone (0.2 ppm) using a randomized crossover study design. All exposures were conducted with subjects engaged in intermittent exercise.	Neutrophil and macrophage numbers in bronchial wash were significantly increased 16 h following ozone exposure when preceded by exposure to diesel, compared to ozone exposure preceded by exposure to filtered air.
Gong et al. (2004a)	13 older adults with COPD (5 M/ 8 F; avg age 68 years); 6 healthy older adults (2 M/4 F; avg age 73 years)	Fine CAPs (Los Angeles); mean concentration 194 μg/m^3 (range 135-229 μg/m^3)	Exposures to CAPs and filtered air (randomized crossover) conducted in an inhalation chamber for 2-h with intermittent light exercise (four 15-min periods). Exposures were separated by at least 2 weeks.	No CAPs-induced respiratory symptoms observed in healthy older adults or older adults with COPD at 0, 4, or 22-h post-exposure. Exposure to CAPs did not significantly affect FVC or FEV_1. CAPs exposure caused a decrease in arterial oxygen saturation 4 h post-exposure which was more pronounced in healthy older adults than in older adults with COPD.
Gong et al. (2004b)	12 adult asthmatics (4 M/8 F; avg age 38 years); 4 healthy adults (2 M/2 F; avg age 32 years)	Coarse CAPs (Los Angeles); 80% of mass between 2.5 and 10 μm, 20% of mass <2.5 μm; mean concentration 157 μg/m^3 (range 56-218 μg/m^3)	Exposures to CAPs and filtered air (randomized crossover) conducted in an inhalation chamber for 2-h with intermittent light exercise (four 15-min periods). Exposures were separated by at least 2 weeks.	No effect of CAPs exposure on spirometry or arterial oxygen saturation was observed 0, 4, or 22-h post-exposure. No respiratory symptoms reported 0-22-h post-exposure in either healthy or asthmatic adults.
Gong et al. (2005)	18 older adults with COPD (9 M/9 F; avg age 72 years); 6 healthy older adults (2 M/4 F; avg age 68 years)	Fine CAPs (Los Angeles) avg concentration 200 μg/m^3; 0.4 ppm NO_2	Each subject was exposed to CAPs, NO_2, CAPs + NO_2, and filtered air for 2-h with intermittent exercise. Exposure order was not fully counterbalanced as NO_2 exposures were conducted after the majority of the CAPs and filtered air exposures had been completed. Exposures were separated by at least 2 weeks.	Exposure to CAPs was observed to decrease maximal mid-expiratory flow and arterial oxygen saturation relative to filtered air 4-22-h post-exposure. This response was more pronounced in healthy older adults than in older adults with COPD. Concomitant exposure to NO_2 did not enhance the response.
Gong et al. (2008)	14 adult asthmatics (9 M/5 F; age 34 ± 12 years); 17 healthy adults (5 M/12 F; age 24 ± 8 years)	Ultrafine CAPs (Los Angeles); mean concentration 100 μg/m^3 (range 13-277 μg/m^3)	Subjects exposed for 2-h during intermittent exercise (15 min periods) to both CAPs and filtered air in random order, with exposures separated by at least 2 weeks.	No significant differences in respiratory symptoms observed between filtered air and ultrafine CAPs exposures. Individuals exposed to higher particle counts tended to experience greater symptoms with CAPs than with filtered air. An ultrafine CAPs-induced decrease in arterial oxygen saturation (0.5%) was observed at 0, 4, and 22-h post-exposure. A decrease in FEV_1 (2%) was also observed 22-h post-exposure relative to filtered air. Responses were not significantly different between healthy and asthmatic adults.
Huang et al. (2003)	38 healthy adults; 36 M/2 F; avg age 26.2 ± 0.7 years	Fine CAPs (Chapel Hill, NC); 23.1-311.1 μg/m^3	Subjects exposed to CAPs (n = 30) or filtered air (n = 8) for 2-h with intermittent exercise (subjects did not serve as their own controls).	The increase in bronchoalveolar lavage fluid neutrophils observed by Ghio et al. (2000) following exposure to fine CAPs was shown to be associated with iron, selenium, and sulfate content of the CAPs.
Kongerud et al. (2006)	17 asthmatic adults (6 M/11 F; avg age 23 years); 46 healthy adults (24 M/22 F; avg age 26 years)	DEP (NIST 1650) both untreated and treated with 0.1 ppm ozone (48 h); 300 μg per nostril	DEP (with and without ozone pre-treatment) were intranasally instilled, using the saline vehicle as control. Subjects did not serve as their own controls (not a crossover design).	Exposure to DEP was not observed to alter markers of inflammation in nasal lavage fluid (e.g., cell counts, IL-8, IL-6) at 4 or 96 h post-instillation.
Larsson et al. (2007)	16 healthy adults; 10 M/6 F; 19-59 years old	Traffic particulates (road tunnel); $PM_{2.5}$: 46-81 μg/m^3; PM_{10}: 130-206 μg/m^3	Exposures were conducted for 2-h with intermittent exercise in a room adjacent to a busy road tunnel. Study used a randomized crossover design with each subject also exposed to normal air (control). Exposures were separated by 3-10 weeks. No exposures to filtered air were conducted.	An increase in bronchoaveolar lavage fluid cell number, lymphocytes, and alveolar macrophages were observed 14 h after road tunnel exposure relative to control. Traffic particulate exposure was not shown to effect cytokine or adhesion molecule expression in bronchial tissues. Respiratory symptoms were reported to increase during exposure to road tunnel air relative to pre-exposure symptom ratings. Exposure to road tunnel air was not shown to affect lung function.
Pietropaoli et al. (2004)	16 asthmatic adults (8 M/8 F), 40 healthy adults (20 M/20 F); 18-40 years old	Ultrafine elemetal carbon; 10, 25, and 50 μg/m^3	Study conducted using a randomized crossover design with 2-h exposures. Asthmatics (n = 16) exposed to filtered air and 10 μg/m^3. 12 healthy adults exposed to filtered air and 10 μg/m^3 at rest; 12 healthy adults exposed to filtered air, 10 and 25 μg/m^3 with intermittent exercise; 16 healthy adults exposed to filtered air and 50 μg/m^3 with intermittent exercise. Exposures were conducted via mouthpiece.	No PM-induced changes in eNO or cell counts, IL-6, or IL-8 in induced sputum were observed in any of the protocols 21-h following exposure. Ultrafine carbon was not observed to increase respiratory symptoms in any of the study protocols. Healthy adults experienced an ultrafine PM-induced reduction in maximal mid-expiratory flow and CO diffusing capacity relative to filtered air 21-h following exposure.

Reference	Subjects	Particle Characteristics	Exposure	Findings
Pourazar et al. (2005)	15 healthy adults; 11 M/4 F; 21-28 years old	DE; PM_{10} concentration 300 µg/m^3	Subjects exposed to DE and filtered air for 1-h with intermittent exercise (randomized crossover study design).	Exposure to DE significantly increased nuclear translocation of NF-κB, AP-1, phosphorylated p38, and phosphorylated JNK in bronchial epithelium 6 h post-exposure.
Pourazar et al. (2008)	15 healthy adults; 11 M/4 F; 21-28 years old	DE; PM_{10} concentration 300 µg/m^3	Subjects exposed to DE and filtered air for 1-h with intermittent exercise (randomized crossover study design).	Exposure to DE observed to enhance epidermal growth factor receptor (EGFR) expression in bronchial epithelium 6 h post-exposure.
Samet et al. (2007)	Ultrafine CAPs: (20 healthy adults; 11 M/9 F; 18-35 years old); Coarse CAPs: (14 healthy adults; 8 M/6 F; 18-35 years old)	CAPs (Chapel Hill, NC): Ultrafine (0.049 ± 0.009 µm); concentration 47.0 ± 20.2 µg/m^3; Coarse (3.59 ± 0.58 µm); concentration 89.0 ± 49.5 µg/m^3	Randomized crossover studies of 2-h exposures (chamber) with intermittent exercise to either ultrafine (n = 20) or coarse (n = 14) CAPs using filtered air as control in both studies. Results compared with previous study of controlled exposure to fine CAPs (Chapel Hill, NC) where subjects did not serve as their own controls (Ghio et al., 2000).	As was shown with fine CAPs, exposure to coarse CAPs increased the percentage of neutrophils in bronchoalveolar lavage fluid 20 h following exposure. Unlike fine CAPs, coarse CAPs did not increase the percent of monocytes in bronchoalveolar lavage fluid. Ultrafine CAPs were not shown to affect any markers of pulmonary inflammation in bronchoalveolar lavage fluid 18 h after exposure. No CAPs-induced changes in lung function were observed.
Schaumann et al. (2004)	12 healthy adults; 4 M/8 F; avg age 27 ± 2.5 years	Fine PM collected (filter) from industrialized and non-industrialized areas in Germany; 100 µg per subject	Bronchoscopic instillation of particles collected from both areas was conducted in contralateral lung segments for each subject.	Particles collected from the industrialized area (transition metal-rich) increased the percentage of monocytes and oxidant radical generation in bronchoalveolar lavage fluid 24-h after exposure compared with PM containing less metal.
Stenfors et al. (2004)	15 asthmatic adults (10 M/5 F; 22-52 years old); 25 healthy adults (16 M/9 F; 19-42 years old)	DE; PM_{10} avg concentration 108 µg/m^3	Subjects were exposed for 2-h with intermittent exercise to DE and filtered air using a randomized crossover study design.	DE was observed to increase neutrophilia and IL-8 in bronchial lavage fluid among healthy subjects 6 h after exposure. Among asthmatic subjects, exposure to DE did not cause an increase in inflammatory markers.

Table C-3. Central Nervous System Effects

Reference	Subjects	Particle Characteristics	Exposure	Findings
Cruts et al. (2008)	10 healthy males; 18-39 years old	DE; particle concentration 300 µg/m^3	Subjects were exposed to DE and filtered air for 1-h at rest in a randomized crossover study design. Exposures were separated by 2-4 days.	Exposure to DE was observed to significantly increase the median power frequency (MPF) in the frontal cortex during exposure, as well as in the hour following the completion of the exposure.

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