PS 4030 Dose- and time-dependent effects of different nickel-based thermal spray coating aerosols on lung toxicity using an animal inhalation model

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Background and Purpose: Thermal spray coating is an emerging occupational process that applies molten metal under pressure onto a surface as a protective coating. Information about the potential health effects and the physio-chemical properties of the aerosols generated during this process are limited. **Methods:** A thermal spray coating generator and inhalation exposure system has been developed to perform animal studies to simulate workplace exposures. Male Sprague-Dawley rats were exposed to three different concentrations of aerosols generated from electric arc wire- thermal spray coating using two nickel (Ni)-based consumable wires- PMET885 and PMET876. Control animals were exposed to filtered air. Total cumulative target concentrations [exposure concentration (C; mg/m^3) x exposure time (T; hr)] for the exposure period were: (1) HIGH–400 mg (25 mg/m^3 x 4 hr/d x 4 d); (2) MIDDLE–80 mg (5 mg/m^3 x 4 hr/d x 4 d); (3) LOW–16 mg (4 mg/m^3 x 4 hr/d x 1 d). At 4 and 30 d after the last exposure, bronchoalveolar lavage (BAL) was performed on the right lung and a histopathological analysis was performed on the left lung to assess lung toxicity. Animal body weights were measured throughout the 30-d post-exposure period to assess general health status of the exposed animals. **Results:** The metal composition of each aerosol was determined by ICP-AES: PMET885 (97% Ni, 2% Al) and PMET876 (56% Ni, 17% Cr, 17% Mo, 5% Fe, 3% Mn). The generated particles were complex metal oxides arranged as chain-like agglomerates with similar mass median diameters of 316 (PMET885) and 367 nm (PMET876). Inhalation exposure to both PMET885 and PMET876 at the HIGH concentration caused a significant loss in body weight compared to the corresponding air controls as soon as 3 and 2 d after the start of the exposure, respectively. Even though the animals in both groups started to gain weight post-exposure, they still weighed significantly less than controls at each time point assessed. Inhalation to both aerosols at the MIDDLE and LOW concentrations had no effect on body weight gain at any time point during and after exposure compared to controls. At all three exposure concentrations and at both 4 and 30 d after the last exposure, BAL fluid lactate dehydrogenase (LDH; lung cell injury marker) and total BAL cells recovered (index of inflammation) were significantly elevated for the PMET885 group compared to air control. BAL fluid LDH was significantly elevated at all three concentrations at 4 d but only at the HIGH concentration after exposure to PMET876 aerosol at 30 d compared to air control, whereas the total BAL cells recovered were significantly elevated at both time points for all three exposure concentrations. Histopathological lung changes after inhalation to the HIGH concentration for both aerosols included alveolar histiocytic infiltration, alveolar interstitial fibrosis, bronchioloalveolar chronic-active inflammation, bronchiolar goblet cell metaplasia, and perivascular mixed cell infiltration. Alveolar interstitial fibrosis was observed in association with inflammatory foci after exposure to the PMET885 aerosol but not PMET876. The incidence of fibrosis in the PMET885 group was higher at 4-d post-exposure compared to 30-d, suggesting the fibrous change was partially reversible and was indicative of a less mature fibrogenesis. In addition, goblet cell metaplasia was observed for both aerosols at 4-d after exposure to the HIGH concentration but not at 30-d. The absence of this change at 30-d after exposure likely indicated a recovery of the bronchiolar epithelium. Inhalation exposure to two different Ni-based thermal spray coating aerosols caused significant lung toxicity and body weight loss in a dose-and time-dependent manner. **Conclusions:** In summary, the PMET885 aerosol that was composed of nearly all Ni (97%) was more pneumotoxic than the PMET876 aerosol that had significant amounts of Cr, Mo, Fe, and Mn besides Ni (56%) in its metal profile. Results of this animal inhalation study indicated that different Ni-based thermal spray coating aerosols can be quite toxic to the lungs, and the varied lung responses observed were likely dependent of the metal composition of the consumables used.

PS 4031 Contributions of TRPA1 and Hypertension in the Cardiovascular Effects of Short-term Exposure to Particulate Air Pollution in Mice

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Background and Purpose: The WHO estimates air pollution causes 7 million premature deaths or about 1 in 8 global deaths. Epidemiological studies indicate that 60-70% of the premature mortality attributed to exposure to air pollution are cardiovascular deaths (CVD) especially in those with pre-existing conditions such as hypertension and heart failure. However, the underlying pathophysiological mechanisms by which air pollution exposure worsen cardiovascular dysfunction are unclear. **Hypothesis:** Because air pollution contains many irritants, we hypothesized that the cardiac toxicity of particulate air pollution ($PM_{2.5}$) exposure depends on activation of the sensory transient receptor potential ankyrin-1 (TRPA1) especially in the setting of hypertension. **Methods:** To test this hypothesis, we combined pollution exposure with a cardiac susceptibility model (angiotensin II, 2.5 mg/kg bwt/day: ANGII osmotic pump) where normotensive and hypertensive male wildtype (WT) and TRPA1-null mice were exposed to filtered air or concentrated ambient $PM_{2.5}$ (CAP) for 3 weeks. **Results:** Mice with ANGII-pumps developed hypertension and cardiac hypertrophy measured as heart weight/tibia length ratio (Hypertensive: WT+Air, 9.6±0.4 mg/mm), and hypertrophy was assessed after CAP exposure in WT (Hypertensive: WT+CAP, 10.2±0.6 mg/mm) and in TRPA1-null mice (Hypertensive: TRPA1-null+CAP, 9.3±0.1 mg/mm; TRPA1-null+Air, 9.7±0.3 mg/mm). These values were significantly greater than matched normotensive, air-exposed control groups (Normotensive: WT+Air, 8.3±0.3 mg/mm: TRPA1-null+Air, 7.9±0.2 mg/mm; Kruskal-Wallis ANOVA on Ranks). Blood pressure (systolic and diastolic; mm Hg) was significantly elevated by CAP compared with air exposure only in hypertensive mice (measured by non-invasive pressure-volume tail cuff). In fact, diastolic blood pressure was positively correlated with cardiac hypertrophy in both WT (r^2 = 0.57) and in TRPA1-null mice (r^2=0.27). **Conclusions:** We describe a unique experiment that both modeled a human susceptibility state of hypertension and tested for a mechanistic role of TRPA1 in mediating the deleterious effects of inhaled particulate air pollution. Although hypertension (induced by ANG II) was worsened by CAP exposure, this effect was neither TRPA1-dependent nor observed in normotensive mice. Thus, hypertension appears to enhance susceptibility to particulate air pollution although the mechanism for this effect remains unknown. This study provides a deeper understanding of the cardiovascular health risks of exposure to particulate air pollution.

PS 4032 Brake-Dustosis: Effects of Brake Dust Exposure on the Murine Pulmonary System following Tracheal Instillation

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Background and Purpose: Particles generated by automotive friction brake pads, commonly referred to as brake dust (BD), come in a range of sizes, shapes, and chemical compositions. These particles play a substantial role in exacerbating urban air pollution. Inhalation of BD is a concern due to its potential health effects, particularly for the respiratory and cardiovascular systems. BD contains a mixture of fine particles and potentially harmful chemicals generated during the braking process, which can adversely affect the respiratory tract upon inhalation. Wild-type mice (C57/b6) were exposed to the coarse fraction of different types of BD particles *in vivo* via tracheal instillation to assess potential adverse pulmonary toxicity. **Methods:** Semi-metallic and ceramic brake dust particles were generated using a custom-built brake dynamometer system and size-selected samples were collected on aluminum substrates using 5-stage cascade impactors. The mass-weighted size distribution of the BD particles was measured using an Aerodynamic Particle Sizer (TSI model 3320). BD particles collected on impactor stage A (aerodynamic diameter 2.5 µm–10 µm) were used for the experiments. C57BL/6J female and male mice were exposed by 5 intra-tracheal instillations of 10 µg/µL BD suspension in phosphate-buffered saline (PBS) delivered over 10 days (250 µg accumulated dose). Instillations of PBS and NIST 1628A (urban dust) suspension in PBS were used as the negative and positive controls, respectively. Non-invasive tail-cuff blood pressure measurements were collected prior to the first instillation and 24 h following the final instillation. Inflammatory responses, DNA damage, and cell counts were assessed in bronchoalveolar lavage fluid (BALF), following the BP measurement. Trace metal analysis on the collected BD particles was performed using ICP-MS while the carbonaceous content was characterized using a standardized NIOSH OC/EC protocol. **Results:** The majority of the mass of aerosolized semi-metallic and ceramic brake dust particles was below 4 µm, while the majority of the number of particles was below 2.5 µm. Exposure to these coarse ceramic and semi-metallic BD particles induced an inflammatory response in both female and male mice, characterized in BALF by increased cell numbers, increased levels of inflammatory cytokines (IL-6 and IL-1β) and increased 8-OHdG production compared to the negative controls. Similar patterns of response in these endpoints were also evident in the urban dust exposed mice. Blood pressure was slightly increased following exposure to brake dust, especially in the female cohort. **Conclusions:** Brake dust (BD) is a major contributor to motor vehicle non-tailpipe particulate emissions and can have detrimental effects on human health. Exposure to BD induced inflammatory and oxidative stress responses in the lungs, and these changes have been associated with increased risks of cardiopulmonary diseases. Specifically, this study investigated the pulmonary toxicity of PM from two different types of brakes in mice using intratracheal instillation. The results showed that both ceramic and semi-metallic BD particles induced significant inflammatory and oxidative responses, similar to the urban dust positive control reference material. Moreover, exposure to BD particles increased blood pressure in both cohorts, especially female mice. These findings suggest that BD particles are biologically active and their potential health risks warrant further investigation. Understanding the composition and health risks associated with brake dust inhalation is essential for public health, and it can provide valuable information for risk management strategies. Future studies should explore the mechanisms of BD-induced toxicity, the effects of chronic exposure, and the potential interventions to mitigate possible adverse outcomes.

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