this study is to identify cellular processes that may contribute to cardiac dysfunction following PM exposure. Isolated neonatal rat ventricular myocytes were cultured for 11 days and then exposed to different concentrations of Zinc (Zn), a soluble component found in many PM samples. Zn significantly decreased spontaneous myocyte beat rate by 15% 2 hrs following exposure and 17% at 4 hrs compared to baseline. Since beat rate is influenced by intercellular communications, fluorescent recovery after photobleaching (FRAP) was then measured. FRAP rate, a physiological measure of cell-to-cell communication and gap junction permeability, was significantly decreased by 76% 4 hrs after exposure but not at 2 hrs. Changes were measured in gene expression of gap junction proteins which mediate communication between myocytes. Exposure of myocytes to Zn for 24 hrs resulted in a 76% increase in mRNA coding for connexin 43. These data suggest that soluble metals found in air pollution particles can affect the ability of cardiac myocytes to spontaneously beat, possibly by disruption of cell-to-cell communication. These effects potentially reflect disturbances in repolarization and impulse propagation which could contribute to PM-associated cardiac morbidity and mortality. This abstract does not necessarily reflect EPA policy.

1446 IRON-MEDIATED AMIODARONE RADICAL FORMATION.

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Numerous adverse effects of amiodarone (AM) may be mediated by free radical species. The current study investigated AM radical formation in microsomal and microsome-free systems. Hamster liver microsomes were incubated with AM, NADPH, and the spin trap α-phenyl-N-t-butylnitrone (PBN). Analysis by electron spin resonance (ESR) spectroscopy revealed a PBN-trapped radical with a triplet of doublets pattern and splitting constant values consistent with those of a carbon-centred radical. Incubation in the absence of NADPH, with microsomes exposed to carbon monoxide, with boiled microsomes, or under anaerobic conditions, did not alter the signal intensity or splitting constant values of the PBN-trapped radical, indicating that cytochrome P450 activity was not required for its formation. However, signal intensity was decreased by addition of the reducing agent sodium dithionite, suggesting a role for iron redox reactions in radical signal generation. Microsome-free incubations with AM and Fe^{2+} sulphate generated a signal pattern with intensity and splitting constant values similar to those in the microsomal incubations, whereas Fe^{3+} sulphate did not generate a measurable signal. Furthermore, the magnitude of the Fe^{2+}-mediated signal was decreased by sodium dithionite or the iron chelator deferoxamine, indicating that Fe^{2+} oxidation to Fe^{3+} is involved in radical generation. Thus, AM radical formation occurs in microsomal and microsome-free systems, and Fe^{2+} appears to play an important role in its generation. (Supported by Canadian Institutes of Health Research grant number MT-13257).

1447 EFFECTS OF SOLUBLE AND INSOLUBLE FRACTIONS OF A STAINLESS STEEL MANUAL METAL ARC WELDING FUME ON FREE RADICAL PRODUCTION AND LUNG INJURY AND INFLAMMATION.

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The goals of this study were to examine the roles of the soluble (Sol) and insoluble (Insol) fractions of a stainless steel welding fume (Tot) collected during manual metal arc welding in the development of rat lung damage and inflammation and correlate those effects with free radical production and metal composition. Welding fume fractions were separated by incubation in saline followed by centrifugation and filtration. Metal composition analysis by energy dispersive spectroscopy revealed both Cr and Mn in the Sol fraction. Using electron spin resonance, the generation of radicals from Cr(VI) was observed, with the highest signal from Tot, an intermediate signal from Sol, and a low signal from Insol. To examine the effects of the fumes on lung damage and inflammation, male Sprague-Dawley rats were intratracheally instilled with Tot at 2 mg/rat, or the equivalent volume of Sol, Insol, or the vehicle (saline). On days 1, 3, and 6, the right lung was assayed for lipid peroxidation (LPO) products while the left lobes were subjected to bronchoalveolar lavage (BAL). LPO was elevated in the lungs following Tot treatment, with most of the effect attributed to the Insol fraction. All fractions caused increases in BAL cell number, including elevated macrophage recovery. However, the Tot and Insol fractions caused increased PMN numbers at days 1 and 3, while the Tot and Sol fractions led to increased eosinophils at day 1. The changes in left lung weight were additive (Sol + Insol = Tot) on day 6, while albumin, total protein, and LDH activity in the first BAL fraction were all additive at day 3. These findings indicate that the ability of the fume to produce free radicals and much of the damage observed in the lungs of rats after Tot treatment depends on both the Sol and Insol fractions of the fume. However, PMN recruitment and LPO were due mainly to the insoluble particulates while eosinophil recruitment was due to the soluble components, most likely soluble metals.

1448 PULMONARY TOXICITY STUDIES WITH TiO2 PARTICLES CONTAINING VARIOUS COMMERCIAL COATINGS.

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Most of the pigment-grade TiO2 samples that have been tested in inhalation toxicity tests have been of the generic variety -(i.e., generally uncoated TiO2 samples or 99% TiO2 and 1% Al2O3). However, questions have been raised over the past twenty years regarding the potential pulmonary toxic effects, if any, of the commercially coated TiO2 materials, generally which contain higher concentrations of aluminum oxide and/or amorphous silica on their surfaces. The aims of this study were to assess in rats, using a well-developed short-term pulmonary bioassay, 1) the acute pulmonary toxicity of several intratracheally instilled commercial coatings on pigment grade TiO2 particles relative to uncoated, TiO2 particle control samples and 2) to bridge the results of these instillation studies with data previously generated from inhalation studies with uncoated TiO2 particles, using the uncoated TiO2 particles as the inhalation/instillation bridge material. Groups of rats were intratracheally instilled with 2 or 10 mg/kg of TiO2 particles containing coatings ranging from 0-7% Al2O3 and/or 0 - 10.5% amorphous silica. Saline-instilled rats served as controls. The lungs of sham and exposed rats were evaluated by bronchoalveolar lavage at 24 hr, 1 week, 1 month and 3 months postexposure (pe). The results demonstrated that the high dose (10 mg/kg) pigment grade TiO2 particles with the greatest Al and amorphous silica coatings produced the most sustained and intense lung inflammatory response, as evidenced by lung cell differentials and BAL fluid levels of LDH and protein, but not alkaline phosphatase. This effect was measured through 1 month but not a 3-month postexposure period. Our bioassay results indicate that the coatings containing the largest concentrations of amorphous silica and aluminum oxide produced the most significant lung inflammatory response but it is important to note that these effects were transient and not sustained. Studies are ongoing to assess the lung tissue responses of rats exposed to the various commercial coatings on pigment grade TiO2 particles.

1449 DEVELOPMENT OF A RAT MODEL OF INHALATION FUME FEVER.

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Occupational fume fevers represent a transient flu-like syndrome in humans associated with the inhalation of freshly formed metal or polymer ultrafine UFP (<100 nm) or fine-sized particles (< 2 mm), notably zinc oxide or PTFE/FEP. Presently, the key physical/chemical features of particulates associated with fume fever are unknown. Some preliminary studies have demonstrated that rats exposed to fine aerosols of ZnO particles or aged, combusted FEP UFP develop a transient lung inflammatory response which seems to mimic fume fever in humans. The development of animal models of fume fever, may provide clues to the mechanism of inflammatory injury occurring in workers following exposures. In preliminary, range-finding studies, rats were exposed to aerosols of zinc oxide (ZnO) particles for a single period of 1 or 3 hours (either 25 or 50 mg/m3), and the lungs of ZnO and sham-exposed animals were evaluated at 24, 72, or 168 hrs (1 week) postexposure using bronchoalveolar lavage fluid (BALF) analyses. Three hour exposures to ZnO at 25 mg/m3 produced a moderate and transient pulmonary inflammatory response (~22% pmns) at 24 hours postexposure, which was reduced at 72 hrs (~10% pmns) and resolved by 1 week postexposure. BAL fluid parameters reflected this minor inflammatory response, as the BAL fluid LDH, protein, and alkaline phosphatase values from the 3 hr ZnO rats were approximately 2X relative to sham controls at 24 hrs pe. Rats exposed to ZnO for 1 hr demonstrated very little response at any time postexposure. Three hour exposures to ZnO at 50 mg/m3 produced a similar pattern, but of greater intensity - i.e., (~45% pmns) at 24 hours postexposure, which was reduced at 72 hrs (~15% pmns) and resolved by 1 week postexposure. BAL fluid LDH, protein, and alkaline phosphatase values in the 3 hr ZnO rats were > 3X relative to sham control values. Studies are ongoing to determine the mechanism of this transient pulmonary inflammatory response, as well as the effects of ultrafine ZnO and PTFE and other metals.

1450 RECOVERY OF MANUAL METAL ARC-STAINLESS STEEL WELDING FUME EXPOSURE INDUCED LUNG FIBROSIS IN SPRAGUE-DAWLEY RATS.

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Welders with radiographic abnormalities of pneumoconiosis have shown a gradual clearing of the x-ray identified effects following removal from exposure. In some cases, pulmonary fibrosis associated with welding fume would appear to a more se-