erature has addressed the issue of identifying the individual component(s) responsible for the adverse effect of inhaled metal working fluid aerosols. The approaches of these toxicology studies have included: 1) the comparison of used versus unused fluids, 2) the addition of individual components/contaminants to the unused fluid, 3) association studies which attempt to correlate and adverse effect with a biomarker such as specific antibodies, and 4) principal component analysis. Each of these approaches has been useful in identifying potential toxic components, but definitive answers to the complex issue of metal working fluid toxicity are still needed.

1102 PULMONARY RESPONSES TO WELDING FUMES: ROLE OF METAL CONSTITUENTS.

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It is estimated that more than one million workers worldwide perform some type of welding as part of their work duties. Epidemiology studies have shown that a large number of welders experience some type of respiratory illness. Respiratory effects seen in full-time welders have included bronchitis, airway irritation, lung function changes, and a possible increase in the incidence of lung cancer. Pulmonary infections are increased in terms of severity, duration, and frequency among welders. Inhalation exposure to welding fumes may vary due to differences in materials used and methods employed. The chemical properties of welding fumes can be quite complex. Most welding materials are alloy mixtures of metals characterized by different steels that may contain iron, manganese, silica, chromium, nickel, zinc, and fluorides. Animal studies have indicated that the presence and combination of different metal constituents is an important determinant in the potential pneumotoxic responses associated with welding fumes. Animal models have demonstrated that stainless steel welding fumes which contain significant levels of nickel and chromium induce more lung injury and inflammation and are retained in the lungs longer than mild steel welding fumes which contain mostly iron. In addition, stainless steel fumes generated from welding processes using fluxes to protect the resulting weld contain elevated levels of soluble metals. These soluble welding fumes have been shown to suppress lung macrophage function and significantly slow the clearance of bacterial pathogens from the lungs after infection. The presence of soluble metals, such as Cr, Ni, and Mn, and the complexes formed by these different metals, as well as fluoride compounds present in fluxes, are likely important in the pulmonary responses observed after welding fume inhalation.

1103 THE ROLE OF BACTERIAL AND FUNGAL CONTAMINANTS IN AGRICULTURAL RESPIRATORY DISEASES.

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Farmers and other agricultural workers face a variety of respiratory diseases including organic dust toxic syndrome (ODTS), farmer's hypersensitivity pneumonitis (HP), asthma-like syndrome, asthma, and pulmonary infections. These diseases arise from complex mixtures of bioaerosols and aeroallergens including pathogenic and non-pathogenic organisms; microbial constituents such as endotoxins and glucans; and allergens from arthropods, animals, plants and molds. ODTS is an acute inflammatory response to inhalation of dusts of organic origin, such as silage, grain dust, cotton dust, and compost. It is characterized by fever, headache, chest tightness, pulmonary infiltrates, and airway obstruction. The bacterial product, endotoxin, and the fungal product, beta-glucan, have been proposed as important etiologic agents in ODTS. Farmer's HP has a similar clinical presentation to ODTS but is an allergic disease caused principally by antigens from thermophilic bacteria. However, proinflammatory constitutents in organic dust may play a role in the disease. Asthma-like syndrome may arise from work in animal confinement units, such as those for intensive poultry and swine production, or from grain handling. This syndrome is an acute non-allergic airway obstruction caused by inflammatory responses to components of the organic dust. It differs from asthma in that it rarely leads to persistent airway hyperreactivity. Pulmonary infections may be zoonotic or may arise from a variety of niche organisms. Human and animal studies elucidating the mechanisms for initiation of pulmonary reactions to organic dusts will be presented. Risk assessment strategies for these mixed exposure environments will also be addressed. Supported by NIEHS P30 ES05605.

1104 EFFECT OF DIESEL EXHAUST PARTICLES (DEP) ON IMMUNE RESPONSES: CONTRIBUTION OF THE ORGANIC COMPONENT.

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The effect of DEP exposure on innate, cellular and humoral pulmonary immunity has been studied using rat, mouse and cell culture models. DEP consist of a complex mixture of petrochemical-derived organics on a carbon core and are regarded as major components of particulate urban air pollution. The alveolar macrophage is considered a key cellular component in pulmonary innate immunity. DEP and DEP organic extracts have been found to suppress alveolar macrophage cytokine (IL-1, TNF-α) and reactive oxygen species (ROS) responses to lipopolysaccharide. DEP depressed clearance of *Listeria monocytogenes* and INFγ-dependent clearance of BCG in a mouse model. INFγ-stimulated nitric oxide (NO) production was suppressed by DEP and DEP organic extract *in vitro*. Further fractionation of the DEP extract suggests that this activity was predominately in polyaromatic containing and more polar (resin) fractions. Organic-stripped DEP did not alter these innate pulmonary immune responses. The contribution of the organic component of DEP is less well defined with respect to acquired and humoral immunity. Indeed, both DEP and carbon black enhanced humoral immune responses (specific IgE and IgG) in an ovalbumin sensitized rat model. It is concluded from a review of the literature and the present work that both the particulate and adsorbed organics may contribute to DEP mediated immune alterations.

1105 EVALUATION OF MCASE-ES USING A TEST PANEL OF PHARMACEUTICAL STRUCTURES.

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Computational models such as the MultiCASE (MCASE) predictive toxicology system are gaining widespread use in academic, industrial and regulatory organizations to assess the potential mutagenicity of new chemical entities. Expanded databases that are the foundation of the expert system (MCASE-ES) have recently become available but the majority of the chemicals within the training set are largely from non-pharmaceutical sources. This system was evaluated using a test panel of 127 structures with known mutagenicity results against the 15 mutagenicity databases available. The evaluation is based on structures within the training set that are reduced to fragments of 2 to 10 atoms in length. MCASE activity values are assigned on the basis of this training set. Predictions based upon the activity value, or CASE unit, quantify the potential activity of the test molecule. We have found the MCASE-ES system to have a sensitivity and specificity of 70% and 60%, respectively, for our test panel. There are several ways in which these results may be improved. For example, we have found that the CASE unit values from true positive predictions exhibited a normal distribution while the CASE unit values from false positive predictions had a multi-modal distribution. This suggests that changes to the logic which link mutagenic activity to the CASE unit may reduce the number of false positive predictions, therefore improving specificity. It was observed that by increasing the CASE unit value associated with mutagenic activity we were able to improve specificity to 88% but resulted in a decrease in sensitivity to 44%. Increasing the number of pharmaceutical compounds present in the training sets, both positive and negative for mutagenicity, and/or appropriately weighing their relevance may improve the sensitivity of this program. This could provide better coverage of pharmaceutical compounds and decrease the number of false predictions.

1106 A YEAST RAD54-GFP GENOTOXICITY ASSAY, IS EFFECTIVE IN IDENTIFYING DIRECT ACTING MUTAGENS IN ADDITION TO CLASTOGENS NOT DETECTED BY BACTERIAL TESTS.

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A eukaroyotic (yeast) genotoxicity assay has been developed which detects increases in the activity of the DNA repair system. It uses a reporter system consisting of the DNA damage inducible promoter of the RAD54 gene fused to a GFP gene. A large study has been carried out to validate the utility of the assay in routine genotoxicity assessment. A single 96 well microplate is used to assess 4 compounds at 9 dilutions, and can be set up by a simple manual protocol for low throughput (<60 compounds/day) or with commercial robotic systems for higher throughput. There are three steps: yeast cells are added to compound dilutions, microplates are incubated overnight, spectrometric data is collected. Optical denisity is used to estimate reduced cell proliferation (toxicity). Fluorescence, normalised for cell density, is used to estimate activity of the repair system (genotoxicity). Data handling protocols are simple and transparent, leading to clear conclusions. Inspection of the data in graphical form allows direct assessment. Less than 0.5ml of compound (1mM) is required and over 250 toxic and non-toxic compounds have been tested, without S9 addition. The results to be presented include the following. Many of 'the usual suspects' are genotox positive in the test: these include EMS, MMS, NQO, MNNG, Cisplatin. Many clastogens are positive in the assay: these include phleomycin, daunorubicin, bleomycin. Expected oxidising agents (methyl viologen, hydrogen peroxide, bleomycin) and aldehydes (crotonaldehyde, benzaldehyde,