1171 Comparative Assessment of *In Vitro* Toxicity Induced by Crystalline Silica and Multiwalled Carbon Nanotubes in Human and Mouse Macrophages

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Pulmonary exposure to particles like crystalline silica (CS) and multi-walled carbon nanotubes (MWCNTs) are known occupational hazards. Once in the lung, these particles activate alveolar macrophages (AM), a first step in the complicated inflammatory cascade and development of diseases. To study the mechanisms involved in particle induced inflammation at the cellular level, human (THP-1) and mouse (RAW 264.7) macrophages were used as *in vitro* models and toxicity of CS and MWCNTs was tested. Cytotoxic dose-responses of each particle were determined at final concentrations of 0.9, 1.8, 3.7, 7.5, 15, 30, 60, 120, 240 and 480 µg/cm^2 for 24-hrs. Both particles caused a dose-dependent reduction in cell viability. Four concentrations pertaining to 0%, 10%, 30% and 60% toxicity for each cell and particle type were chosen for cytokine analysis: 41 markers in THP-1 and 32 markers in RAW 264.7 were measured. Activation of inflammasome cascade (IL18), pro-inflammatory markers (TNF-α), dysregulation (IL6) and fibrotic markers like growth factors, some of which play an important role in fibrosis, were observed. Cytokines involved in inflammation (IL1-B, IL18) and cell recruitment (MCP-1, MIP) were found to be elevated. Based on TH1/TH2 (IL18/IL4) ratio, there was a concentration-dependent polarization to TH1 response. Overall, THP-1 cells produced a greater inflammatory response to particle exposure than RAW 264.7 cells and MWCNTs were more potent than CS. Data clustering showed MWCNTs and CS treated THP-1 and RAW cells had 24 and 7 common cytokines, respectively, and 11 cytokines were found to be common between both cell lines and particle types. Principle component Analysis showed that the response, at same doses can be easily distinguished between particle type and was more apparent in THP-1 than RAW cells. In conclusion, both particle exposures resulted in significant cytotoxicity as well as production of inflammatory mediator in a concentration-dependent manner. However, THP -1 cells were more responsive than RAW cells and the potency of MWCNTs observed was much higher compared to silica at equal mass in both cell types, possibly due to difference in particle size and also due to difference in ASC inflammasome/casp1 activation cascade between two cell types. Ongoing transcriptomic studies may further differentiate the mechanisms of particle toxicity in different types of macrophages.

1172 *In Vitro* Toxicity Comparison of Surrogate Metal Oxides Found in Welding Fumes

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Welding fumes were classified as a Group 1 carcinogen (*carcinogenic to humans*) in 2017 by the International Agency for Research on Cancer based on sufficient epidemiological evidence and limited evidence in experimental animals. Toxic metals commonly found in the fumes are chromium (Cr), iron (Fe), and nickel (Ni). Copper (Cu)-based welding consumables are currently being investigated as a less toxic alternative. The objective of this study was to evaluate the acute toxicological potency of a new Cu-Ni welding fume in human bronchial epithelial cells (BEAS-2B) over a wide dose range (0, 1.56, 3.13, 6.25, 12.5, 25, 50 and 100 µg/ml). The primary components of the welding fume were also assayed to determine their relative potencies and included nickel (II) oxide (NiO; <10 µm and <50 nm sizes), copper (II) oxide (CuO; <10 µm and <50 nm sizes), and iron (III) oxide (Fe_2O_3; <5 µm). Physicochemical properties including dissolution were determined for the welding fume and its components. Membrane damage and cell proliferation/viability were quantified by measuring lactate dehydrogenase (LDH) release and conversion of the tetrazolium salt, WST-1, respectively after 24 h of exposure. The acellular oxidative potential of the welding fume and its component metals was determined by electron paramagnetic resonance. Cellular oxidative stress was measured via flow cytometry using change in CellROX. Experiments were run in a randomized complete block design (n=3 independent blocks) with a one-way layout of treatment combinations. The data showed that CuO (<50 nm) and Cu-Ni fume were the most toxic, and significantly increased LDH levels and decreased cell proliferation/viability with increasing concentrations *in vitro*. NiO (<50nm) was of intermediate toxicity primarily decreasing cell proliferation/viability at the higher doses with no significant effect on LDH levels. At equal mass, the nanocomponents were more toxic compared to their micron-sized components. No significant effects for damage and proliferation/viability were found for the other metal oxides tested. CuO (<10 µm and <50 nm sizes) and the Cu-Ni fume resulted in significant acellular and cellular levels of oxidative stress while the other metal oxides had no significant effect. These results suggest that the Cu-Ni fume has the potential to be inflammatory and toxic *in vivo*, and this effect may be primarily driven by the Cu component.

1173 *In Vitro* Toxicity Assessment of Respirable Solid Surface Composite Sawing Particles

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Solid surface composites (SSC) are a class of popular construction materials composed of aluminum trihydrate (ATH) and acrylic polymers. Previous investigations have demonstrated that sawing SSC releases substantial airborne dusts ranging size from 6 nm to 19.8 µm, with a geometric mean diameter of 1.05 µm. In mice, aspiration exposure to airborne SSC dusts induced symptoms of pulmonary inflammation at 24 h post-exposure: neutrophilic influx, alveolitis, and increased lactate dehydrogenase (LDH) and proinflammatory cytokine levels in lavage fluid. The particles appeared to be poorly-cleared, with 81% remaining at 14 days post-exposure. The objective of this study was to determine the toxicity of specifically respirable-sized particles on a model of human alveolar macrophages (THP-1). The relative toxicities of sub-fractions (0.07, 0.66, 1.58, 5.0, and 13.42 µm diameter) of the airborne particles were also determined. THP-1 macrophages were exposed for 24 h to respirable particles from sawing SSC (0, 12.5, 25, 50, or 100 µg/ml), or size-specific fractions (25, 50, and 100 µg/ml). Respirable particles decreased viability by 15% and 19% after exposure to 50 µg/ml and 100 µg/ml SSC, respectively, which correlated with increased cell culture supernatant LDH activity by 40% and 70% when compared to control. Reactive oxygen species (ROS) production were increased by 64% and 106% after exposure to 50 µg/ml and 100 µg/ml, and the glutathione peroxidase activity was increased by 22%, 18%, and 20% at the 12.5, 25, and 50 µg/mL exposure levels, respectively. IL-1β, IL-2, IL-4, IL-10, IL-12p70, IL-13, IFNγ, and TNFα were all increased in a dose-dependent manner. In the cells exposed to sub-fractions of SSC particles, at 50 µg/ml, the 0.07µm particles killed 23% of cells. At 100 µg/ml, 0.07 and 1.58 µm particles killed 36%, and 22% of cells, respectively. While each of these described fractions elicited a significant LDH response from control, they were not statistically different from each other. These results indicate a potential for cytotoxicity of respirable SSC particles and a relationship between particle size and toxicity.

1174 Identification of IL-17 Pathway as a Plausible Target for Pulmonary Effects following Acrolein Exposure Studies on Inbred Mouse Strains and Human Primary Bronchial Epithelial Cells at Air-Liquid Interface

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Acrolein is an important constituent of e.g. cigarette and biomass smoke. Chronic inhalation exposure has been associated with lung diseases like asthma and chronic obstructive pulmonary disease. Inter-strain variability in inflammatory response and oxidative stress was evaluated in seven inbred mice strains (129S1/SvImJ, A/J, BALB/cByJ, C3H/HeJ, C57BL/6J, DBA/2J, and FVB/NJ, females 12-14 weeks old) exposed to 0 or 1 ppm acrolein for 11 weeks (6 h/d, 5 d/wk). The *in vivo* experiments were followed up by acute exposure *in vitro* (0, 0.1 and 0.2 ppm acrolein, 30 min) using human primary bronchial epithelial cells (PBEC) cultured at air-liquid-interface (ALI). *In vivo*, total cell numbers in broncho-alveolar lavage and protein concentrations was unaffected by acrolein in all mouse strains. BALB/cByJ, C57BL/6J, and 129S1/SvImJ were the most affected strains with significantly increased expression of oxidative stress, pro-inflammatory and/or tissue injury markers. Both *Mmp9* and *Timp1* were significantly upregulated in the strains DBA/2J, C3H/HeJ and FVB/NJ indicating a change in protease-anti-protease balance. Upregulation of *Il17b* in the susceptible strains mice led us to investigate the pro-inflammatory IL-17 pathway genes in the PBEC-ALI model. *In vitro*, significantly increased expression of *IL17A, C and D*; *IL1β, IL22*, and *RORA* was detected in the PBEC-ALI following exposure to 0.1 and 0.2 ppm acrolein. The inter-strain differences in response to sub-chronic exposure to acrolein suggest that genetics may play a role in the pulmonary response to acrolein. Additionally, acrolein exposure mediated alteration of key IL-17 pathway genes in the PBEC-ALI model, which identifies IL-17 as a plausible candidate pathway warranting further mechanistic studies.

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and Scientific Sessions of the 59th Annual Meeting of the Society of Toxicology, held at the Anaheim Convention Center, Anaheim, California, March 15–19, 2020.

An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 542.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 580.

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