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Evaluation of $PM_{2.5}$-induced antioxidant consumption and ROS generation as a Proxy for the Aerosol Toxicity

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In recent decades, oxidative potential (OP) has emerged as an alternate metric of $PM_{2.5}$ toxicity. Although there are several ways to assess OP, ROS generation and antioxidant depletion measurements are the most widely used methods. However, the biological significance and the relationship among different OP measurements has not been explored at a large spatial scale. In this study, we evaluated this relationship using a large number of ambient $PM_{2.5}$ samples (N=385) collected from 14 different sites across 4 different continents and using 5 different endpoints [3 acellular (OP^{DTT}, $OP^{GSH}$and OP^{OH}) and 2 cellular endpoints (cellular ROS and cytotoxicity using A549 cells)] to assess the cytotoxicity and OP of water-soluble $PM_{2.5}$ extracts. Our results show that among the different endpoints measured, only cytotoxicity and cellular ROS response show a consistently strong correlation ($r > 0.5$) across different sites. However, both cellular ROS response and cytotoxicity were poor to moderately correlated ($0.11 < r < 0.41$) with the acellular OP endpoints. We next attempted to explain the observed statistical relationships between OP and cytotoxicity using a subset of the data (Midwest US) and mechanistically investigating the role of antioxidants in cytotoxicity and ROS consumption. We pre-treated the A549 cells with two different antioxidants [glutathione (GSH) and ascorbic acid (AA)] and measured the intracellular GSH depletion, cellular ROS generation and cytotoxicity, caused by $PM_{2.5}$ extracts. Interestingly, pre-treating the cells with GSH/AA resulted in a substantial decrease (>50 %) in both ROS response and cytotoxicity and pre-treating cells with AA reduced GSH consumption of the cells indicating a protective role of AA against depletion of intracellular GSH reserves. However, neither cytotoxicity, nor cellular ROS response was strongly correlated with intracellular GSH depletion. These results indicate that antioxidants play a collective role in the cellular process and therefore, oxidative stress and OP measurements could be more representative of $PM_{2.5}$ toxicity, if existing practices are modified to include measurement of specific ROS species and the interaction between different antioxidants.

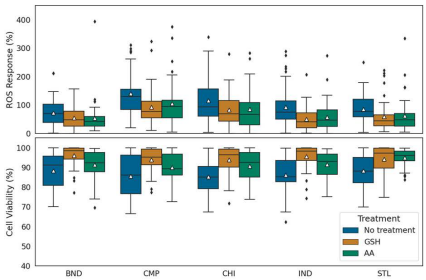

Figure 1: Effect of antioxidant treatment on cellular ROS response and cell viability. White triangles represent mean. The box contains the 25–75th percentile of the measurements, the center line of the box denotes the median, and the whiskers denote 1.5 times the interquartile range of the respective endpoints. BND= Bondville, CMP = Champaign, CHI = Chicago, IND = Indianapolis and STL = St Louis

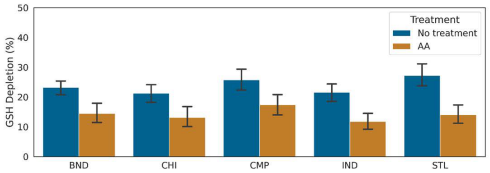

Figure 2: Effect of AA pre-treatment on intracellular GSH depletion at various sites in the Midwest US. BND= Bondville, CMP = Champaign, CHI = Chicago, IND = Indianapolis and STL = St Louis