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## **$^1\text{H}$ NMR-based metabolomics study on repeat dose toxicity of fine particulate matter in rats after intratracheal instillation.**

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### Abstract

Systemic metabolic effects and toxicity mechanisms of ambient fine particulate matter ( $\text{PM}_{2.5}$ ) remain uncertain. In order to investigate the mechanisms in  $\text{PM}_{2.5}$  toxicity, we explored the endogenous metabolic changes and possible influenced metabolic pathways in rats after intratracheal instillation of  $\text{PM}_{2.5}$  by using a  $^1\text{H}$  nuclear magnetic resonance (NMR)-based metabolomics approach. Liver and kidney histopathology examinations were also performed. Chemical characterization demonstrated that  $\text{PM}_{2.5}$  was a complex mixture of elements. Histopathology showed cellular edema in liver and glomerulus atrophy of the  $\text{PM}_{2.5}$  treated rats. We systematically analyzed the metabolites changes of serum and urine in rats using  $^1\text{H}$  NMR techniques in combination with multivariate statistical analysis. Significantly reduced levels of lactate, alanine, dimethylglycine, creatine, glycine and histidine in serum, together with increased levels of citrate, arginine, hippurate, allantoin and decreased levels of allthreonine, lactate, alanine, acetate, succinate, trimethylamine, formate in urine were observed of  $\text{PM}_{2.5}$  treated rats. The mainly affected metabolic pathways by  $\text{PM}_{2.5}$  were glycine, serine and threonine metabolism, glyoxylate and dicarboxylate metabolism, citrate cycle (TCA cycle), nitrogen metabolism and methane metabolism. Our study provided important information on

assessing the toxicity of PM<sub>2.5</sub> and demonstrated that metabolomics approach can be employed as a tool to understand the toxicity mechanism of complicated environmental pollutants.

*KEYWORDS:*

Fine particulate matter; Metabolites; Metabolomics; Pathway analysis; Rats; Toxicity