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## **Mechanisms of Arsenite's Effect on Polycyclic Aromatic Hydrocarbon (PAH) Induction of Human Cytochrome P450 1A1**

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PAHs and heavy metals are often co-contaminants. The primary human health hazard of PAHs is carcinogenicity; a consequence of bioactivation to reactive intermediates by the CYP1 enzyme family, which is also induced by PAHs. Heavy metals, such as arsenic, may affect CYP1A1 enzyme induction, thereby altering the potential carcinogenicity of PAHs. Thus, effects of heavy metals on the PAH-mediated induction of CYP1A1 mRNA expression and protein activity were studied in human HepG2 cells lines. To identify transcriptional and translational effects, quantitative Real Time RT-PCR and EROD assays were used with HepG2 cells treated with 5uM each of the PAH, benzo[k]fluoranthene (BKF) and arsenic separately, and as a mixture. Vehicle and arsenic did not induce CYP1A1, while BKF and As markedly decreased BKF-mediated induction of CYP1A1 mRNA, but to a lesser extent than the decrease in enzyme activity. We conclude that transcriptional effects of arsenic on CYP1A1 expression are mediated via factors at a characterized oxidative response region upstream of the promoter, independently of the Ah receptor. Additionally, Heme Oxygenase-1, responsible for the initial, rate-limiting reaction of heme degradation with some CYPs is induced by arsenic, and this provides a mechanism for post-translational regulation.

