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DISSERTATION TITLE: *CYP1A1 and CYP1B1 in human lung. PAH-bioactivation capacity, sex differences and steroid receptor mediated regulation.*

Men and women may experience unequal susceptibility when exposed to airborne environmental pollutants and sex hormones are implicated to play a role in such differences. Studies have indicated that women may be at greater risk of developing lung cancer than men, and this has been associated with an increased susceptibility to carcinogens in tobacco smoke.

Polycyclic aromatic hydrocarbons, PAH, are widespread toxicants typically present in urban- and industrial air and tobacco smoke. Several PAH are classified as human carcinogens, and inhalation exposure is directly linked to an increased risk of lung cancer through acquired DNA-damage (formation of DNA adducts). If lung cells fail to repair such DNA adducts, mutations may arise in important genes which normally instruct the cells when to multiply, and this may lead to lung cancer.

PAH are non-reactive chemicals that easily pass through the cell membrane. Inside the cells, they are bioactivated to DNA-damaging compounds by the cell`s enzymes (CYP1A1 and CYP1B1). Gene expression of CYP1A1 and CYP1B1 in lung cells may influence susceptibility to the harmful effects of PAH in humans.

We carried out experiments to analyze and establish the individual contributions of CYP1A1 and CYP1B1 in bioactivation of the PAH compound, benzo[*a*]pyrene (B[*a*]P). Furthermore, we have analyzed whether or not established lung cell lines display sex differences in expression of these enzymes, and if expression could be influenced by sex hormones and their receptors. The results provided by our experimental work suggest that CYP1A1 plays a major role in bioactivation of B[*a*]P in human lung cells. Furthermore, our findings reveal that female lung cells display both significantly higher expression of this enzyme and significantly higher levels of acquired DNA-damage upon exposure to PAH. We also show that sex hormones and their receptors alter the expression of CYP1A1 and CYP1B1 in human lung cells, and thus may be involved in the observed sex difference in CYP1A1.

Altogether, our studies provide new evidence indicating that PAH present in tobacco smoke and air pollution may be more harmful to the female lung than the male lung, and that sex hormones may play a role in these observed differences in PAH-susceptibility between men and women.