

Species Differences in Naphthalene Toxicity: Implications for Humans

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Naphthalene administration results in highly selective necrosis of nonciliated bronchiolar epithelial cells of mice regardless of the route of administration. Inhaled concentrations of 2-5 ppm for 4 hrs, well below the current occupational standard, cause detectable toxicity. In contrast, injury to airway epithelium of the rat does not occur at concentrations up to 100 ppm. The nasal epithelium of both rats and mice is highly sensitive to naphthalene administered either parenterally or by inhalation. Recent studies have demonstrated sensitivity of rat olfactory epithelium at concentrations similar to those in urban atmospheres (0.3 ppm). Human exposure to naphthalene is nearly universal; the recent NHANES studies demonstrated detectable levels of 1-naphthol glucuronide in the urine of all 2785 subjects tested. However, epidemiologic studies have failed to draw a relationship between naphthalene exposure and any long term health consequences in the respiratory tract. Either humans are not as susceptible to the compound as rodents or respiratory diseases are multifactorial in origin and epidemiologic studies have not been sufficiently powered to detect subtle contributions of naphthalene to the overall incidence of disease. These species differences in susceptibility to naphthalene toxicity underscore the need to develop biomarkers that are tightly tied to the mechanisms of toxicity and which will be applicable in human populations.

The species, tissue and site selective injury caused by naphthalene have been used as a means of identifying mechanisms associated with toxicity. Naphthalene undergoes metabolism by the cytochrome P450 monooxygenases to reactive metabolites which become bound covalently to tissue proteins. The primary P450 involved in metabolism in the mouse lung and rat nose appears to be CYP2F; this protein has high affinity for naphthalene as a substrate ($K_m \sim 4 \mu M$) with high catalytic turnover (104 min^{-1}). CYP2F orthologues found in the lungs of non human primates and humans, had little or no catalytic activity when expressed as recombinant enzyme. This was consistent with the finding that lung microsomes from monkeys and humans metabolized naphthalene to water soluble metabolites at very low rates and that monkey dissected airways generated metabolites very slowly. Since the initial step in the turnover of naphthalene is critical to toxicity, these data would argue that monkeys and humans would be considerably less susceptible than rodents to naphthalene exposure. However, more recent data have shown that, while the rates of water soluble metabolite formation are low, reactive metabolite protein binding occurs at similar levels in sensitive rodent tissues and in dissected airways. We have identified a number of adducted proteins in tissues of the rodent and monkey and are using a number of different approaches to identify which are important to the necrotic lesions associated with naphthalene exposure. We are also developing a number of approaches for examining adducts in exposed human populations.

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