Ethylene-Induced Nasal Lesions in Rats: Understanding the Pathogenesis and the Impact for Human Risk Assessment

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Abstract

In 2008 a GLP-compliant, guideline subchronic (13-wk) inhalation toxicity study of ethylene was conducted in F344\DuCrl rats, with target exposure concentrations (0, 300, 1000, 3000, and 10,000 ppm) based on expected saturation kinetics for the metabolic conversion of absorbed ethylene to the reactive intermediate ethylene oxide. Biomarkers of exposure (HEVal hemoglobin adduct levels) and effect (micronucleus formation) were evaluated in addition to standard endpoints. Repeated inhalation of up to 10,000 ppm ethylene resulted in increased HEVal levels that were roughly proportional to exposure concentration with a plateau effect observed at the highest concentrations and no evidence of cytogenetic damage or systemic toxicity. Histopathologic observations were limited to the upper respiratory tract. Rats exposed to ≥ 300 ppm ethylene had eosinophilic rhinitis with mucous cell hyperplasia/hypertrophy (MCH) and hyalinosis in the nasal respiratory epithelium. This previously unreported nasal lesion was distinct from that reported in rats exposed to ethylene oxide and has been confirmed in subsequent studies in F344 and Wistar rats. To investigate time- and concentration-dependent effects of ethylene exposure F344 rats were exposed to 0, 10, 50, 300, or 10,000 ppm ethylene for up to 4 weeks. Standard toxicological parameters, serum IgE, IgG1, and IgG2a levels, and regional alterations in nasal mucosal gene expression and morphologic alterations were evaluated. Concentration- and time-dependent effects of ethylene exposure on the time of appearance and severity of eosinophilic inflammation and MCH in nasal airways were observed. The data indicate that cell death and secondary epithelial regeneration was not a part of the pathogenesis of the ethylene-induced epithelial and inflammatory responses and that the lesion is reversible in the absence of continued exposure. No increase in total serum IgE or IgG isotypes were measured suggesting that the ethylene-induced nasal lesion does not involve a systemic immune-mediated antibody response. Regional and time-dependent enhanced gene expression of Th2 cytokines (e.g., IL-5, IL-13), Ym1/2 (chitinase) and genes related to increased airway mucus production and secretion (Gob2, Muc5AC) were observed. The mechanisms by which ethylene induces these morphologic and molecular responses has yet to be determined. Studies employing episodic exposures to ethylene, a respiratory sensitizer (*o*-Phthalaldehyde; OPA) and an irritant gas (ozone) are being conducted to assess the role of innate and adaptive immunity in the development of ethylene-induced eosinophilic rhinitis and MCH in the nasal respiratory epithelium of rats. These mode of action studies are key to understanding the pathogenesis, relevance and impact of the ethylene-induced nasal epithelial remodeling observed in rats for assessing the risks to human health from ethylene exposure.