Mode-of-Action Evaluation for Lung Tumors in Mice Exposed to Ethylene Oxide via Inhalation

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Ethylene oxide (EO) is a direct acting mutagen and a rodent carcinogen, but it is uncertain whether EO is carcinogenic through a mutagenic mode of action (MOA). To address the MOA for mouse lung tumors, an integrated study was conducted evaluating a variety of biomarkers related to oxidative stress, DNA reactivity/ breakage, mutations in a reporter (cII) and endogenous (K-ras) gene, and cell proliferation as putative key events, in the target tissue. The dose response and temporality for these key events was assessed in male B6C3F1 mice exposed to 0, 10, 50, 100, or 200 ppm EO (4 weeks) or 0, 100, or 200 ppm EO (8 or 12 weeks) by inhalation (6 hours/day, 5 consecutive days/week). Results indicate that: (1) EO does not appear to cause the lung tumors primarily via its DNA reactivity, since a sustained increase in cII MF was not seen at 100 ppm (which produced substantial increases in lung tumors in the mouse NTP study), and the increase at 200 ppm was only weak. (2) Oxidative stress is likely to play a multifaceted role in the tumorigenic process, in light of the absence of an effect on 8-OHdG adducts, and the observed mutation spectra of K-ras codon 12 and cII. The role of EO-induced DNA adducts in the etiology of the observed mutations needs further elucidation. (3) The available data on cell proliferation and K-ras mutations support a MOA that includes effects on intracellular signaling pathways and selection of preexisting K-ras mutant cells, as well as an interplay between oxidative stress and RAS activation. These results suggest a complex multi-faceted MOA, potentially involving EO action at multiple steps along the pathway to tumor development.