Draft Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE): Rat Liver Carcinogenicity

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Rat Liver Tumors Are Not Quantitatively Relevant to Human Cancer Hazard or Risk

- Rat liver tumors observed only by inhalation exposure to 5000 ppm ETBE
  - Substantially exceeds exposure for onset of nonlinear toxicokinetics (approximately 1500-2000 ppm)
  - No liver tumors or preneoplastic lesions at 1500 ppm
  - EPA and OECD guidance cautions that toxicity and tumors above a threshold for nonlinear toxicokinetics are not a quantitatively human relevant hazard or risk
- Had the rat inhalation study been designed using EPA and OECD toxicokinetic dose selection guidance, ETBE would not have been identified as a rodent carcinogen

Cancer Descriptor of "*not likely to be carcinogenic in humans*" is Justified for ETBE

- **EPA *Preamble to IRIS Toxicological Reviews* notes this descriptor is justified when "convincing evidence that effects are not likely…*below a defined dose* [emphasis added]" is available**
  - No tumorigenicity at non-saturating 1500 ppm dose
  - Mode of action investigations indicate biological effects (e.g., CAR/PXR/PPARα activation; oxidative stress) are limited to doses exceeding onset of nonlinear toxicokinetics
- **Occupational ETBE exposures deliver a systemic acetaldehyde dose equivalent to consumption of less than one drop of beer.**