

IRIS Review of Tertiary Butyl Alcohol (TBA) and Ethyl Tertiary Butyl Ether (ETBE)

Samuel M. Cohen, M.D., Ph.D.
Department of Pathology & Microbiology
Havlik-Wall Professor of Oncology
University of Nebraska Medical Center
Omaha, NE 68198-3135

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Involvement with ETBE

- Served on Pathology Working Group (PWG) evaluating rat kidney effects

Effects of ETBE on Rat Kidney

- Same issues as for TBA
- All effects are due to α_{2u} -globulin nephropathy, chronic progressive nephropathy (CPN) and cortico-medullary calcification
- None of the kidney effects are relevant to humans
- Should not be considered for risk assessment

ETBE Effects on Rat Liver

- Early: Centrilobular hypertrophy
- Late: Increased incidence of tumors (adenomas)
Males only, by gavage or inhalation but not by drinking water

Centrilobular Hypertrophy

- Related to nuclear receptor activation (CAR, PXR, PPAR α)
- Occurs early (days to weeks)
- Not present in two year study
- This combination of findings is usual as centrilobular hypertrophy does not persist through 2 years
 - Maronpot et al., Toxicol. Pathol., 38: 776-95, 2010
- Due to metabolic effects of nuclear receptor activation
- Most data suggests PPAR α activation

Relevance to Humans of Rat Liver Findings

- Centrilobular Hypertrophy occurs in rats, mice, dogs, monkeys, humans
 - Secondary to metabolic effects of nuclear hormone activation
 - Requires high doses
- Tumors are not relevant to humans
 - Increased hepatocellular proliferation in rats
 - No increased proliferation in monkeys or humans
 - Epidemiology studies for phenobarbital (CAR) and fibrates (PPAR α) are negative
 - Corton et al., Crit. Rev. Toxicol., 44: 1-49, 2014 (PPAR α)
 - Elcombe et al., Crit. Rev. Toxicol., 44: 46-82, 2014 (CAR, PXR)

Concerns About Systematic Review of ETBE Literature (Examples)

- Quality of studies
 - Lack of critical evaluation of literature regarding experimental details and interpretations
 - Lack of knowledge about key concepts described in article (e.g. pathology, MOA)
- Kidney – Acharya et al.
 - Toxic effects at doses not toxic in NTP study
 - Concern about infections of animals
- Liver initiation-promotion studies
 - Complex protocols
 - Inconsistent findings
 - Bladder tumors with 5 chemical protocol but not with bladder specific (BBN) protocol
 - Large variability in tumor incidence with 5 chemical treatment without test chemical exposure (“controls”)

Conclusions

- ETBE findings in rat kidney are not relevant to humans, and should not be used for human risk assessment
- ETBE tumor findings in rat liver are not relevant to humans, and should not be used for human risk assessment
- ETBE centrilobular hypertrophy findings in rat liver are potentially relevant to humans at high exposures and could be used for human risk assessment