



# **Draft Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE): 2-Stage Carcinogenicity Studies**

**IRIS Public Meeting**

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**B. Bhaskar Gollapudi, Ph.D, Exponent, Inc.**

**Representing: LyondellBasell**



## 2-Stage Rat Oral Carcinogenicity Studies:

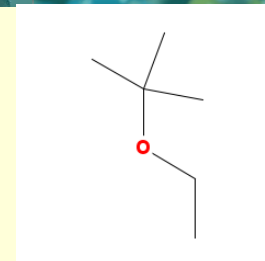
- Initiate tumorigenesis by treatment with high doses of mutagenic carcinogens
- Promotion by treatment with high doses of ETBE for 19 -31 weeks
- e.g., Hagiwara et al. 2011, Liver Tumor Promotion Study:

ETBE (mg/kg/d)	% Aden. or Carcinomas
Initiated + 0	3
Initiated + 300	3
Initiated + 1000	20
Uninitiated +0	0
Uninitiated + 1000	0

- **ETBE is not an initiator,**
- **ETBE promoted tumors at a dose exceeding metabolic saturation,**
- **Promotion activity has a threshold,**
  - **Tumor promotion likely through nuclear receptor activation.**



## ETBE Genotoxicity Profile



- Uniformly negative for all apical genotoxicity endpoints

No.	Study Type	Endpoint Investigated	Result
1	Bacterial Reverse Mutation Assay	Gene Mutation	Non-genotoxic
2	In vitro CHO/HPRT assay	Gene Mutation	Non-genotoxic
3	In vitro chromosomal aberration assay in CHO cells	Clastogenicity	Non-genotoxic
4	In vivo assays for cytogenetic damage (Total of 7 assays)	Clastogenicity and aneugenicity	Non-genotoxic