ToxStrategies

Draft Toxicological Review of *ETBE*

Topic 3: Use of 2-stage carcinogenicity bioassays

Susan Borghoff PhD, DABT; Comments on behalf of LyondellBasell
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Innovative Solutions
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Topic 3. Use of 2-stage carcinogenicity bioassays

- Lifetime inhalation, but not oral, ETBE exposure has been associated with increased liver adenomas and carcinomas in male F344 rats.

- Toxicokinetic analysis comparing oral and inhalation exposures from these studies on the basis of metabolized dose of ETBE or TBA indicated that these studies yielded comparable internal concentrations which suggests that the lack of carcinogenic effects via oral exposure is not likely due to a difference in administered dose.

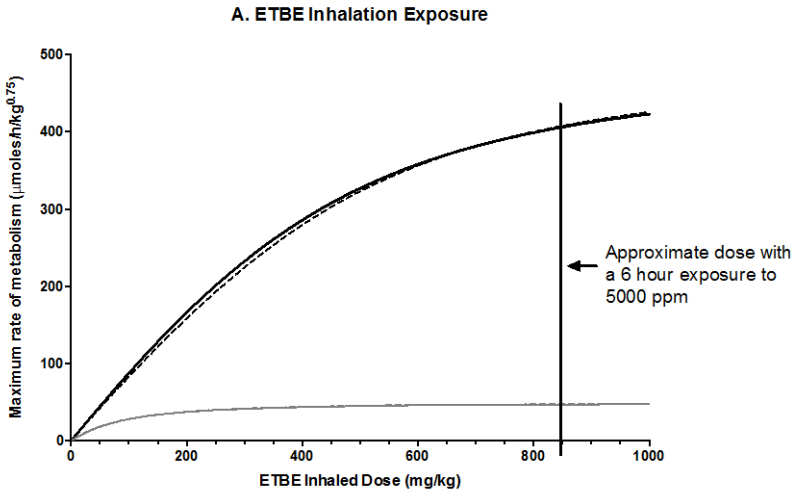
  - The difference in response is likely due to both the administered dose and rate at which the ETBE dose is delivered.

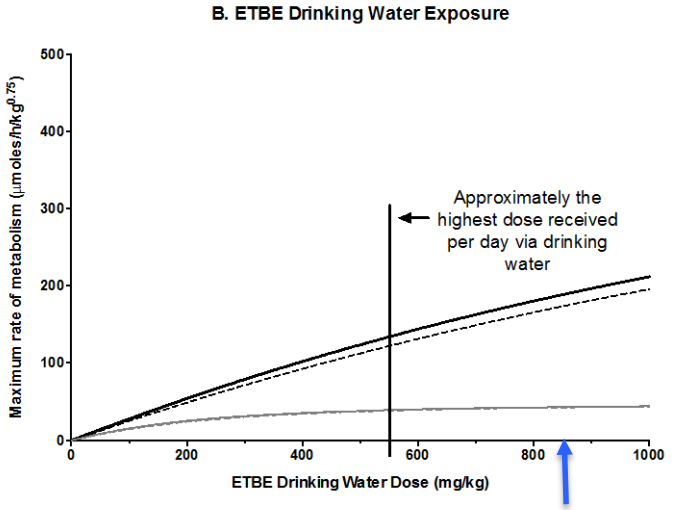
- Notably, sub chronic oral ETBE exposure increased 2-stage mutagen-initiated carcinogenesis in several tissues, including the liver, as such the 2-stage initiation-promotion bioassays were decisive in extending the weight of evidence descriptor to the oral route.

  - The 2-stage mutagen-initiated studies support the ability of ETBE to act as a promotor of carcinogenesis.

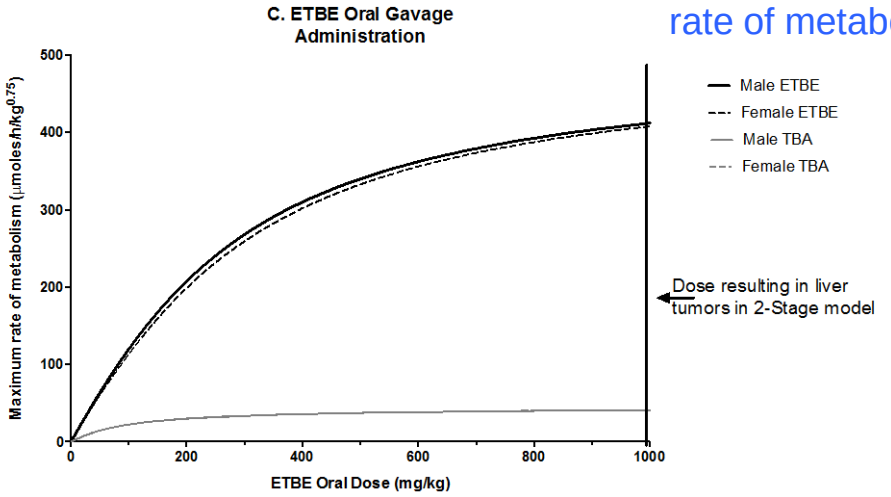
  - No liver tumors were identified in a standard drinking water 2-year study conducted in rats, a route of administration that is more relevant than oral gavage.

Model simulations of rate of ETBE and TBA metabolism under different exposure scenarios; Dose and dose rate





Dose comparable to inhalation and oral gavage shows lower rate of metabolism that is not saturated.



Borghoff et al., 2016 (in press)

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