Draft Toxicological Review of *t*-Butanol: Disentangling mechanisms of kidney toxicity and carcinogenicity: Public Comment: LyondellBasell

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G C Hard Report on TBA to LyondellBasell, 2005
GC Hard, RH Bruner, SM Cohen, JM Pletcher, KS Regan
Regulatory Toxicol Pharmacol, 2011

13-week toxicity study – male rats

- Hyaline droplet accumulation - angular droplets
- Granular cast precursors present at OSOM-ISOM border
- Granular casts seen in specially-stained kidneys

Two-year carcinogenicity study

15-month interim sacrifice – male rats

- Linear papillary mineralization (LPM) present

Two-year terminal sacrifice

- LPM in most tumor-bearing male rats
- Most rats with tumors or ATH had advanced CPN
- CPN severity in males linked to tumors
  - 3.5 versus 2.9

- Absence of chemical-related nephrotoxicity in both sexes
- Hyperplasia of papilla lining a component of CPN

CONCLUSIONS

- **The α2u-g nephropathy evidence is not "limited" but relatively robust**
- **Tubule cell exfoliation necessitates compensatory regeneration**
- **The only responses to TBA in rat kidneys are α2u-g nephropathy in males and exacerbated CPN**
- **Individual animal evidence is sufficient to support advanced CPN as contributing to the RTT response**
- **TBA male rat renal tumors are adequately explained by α2u-g nephropathy combined with advanced CPN**

- **Transitional cell hyperplasia in the TBA study is not a nephrotoxic response**
- **Suppurative inflammation is not a nephrotoxic response but caused by bacterial infection**

TBA – Female rat – High dose

Transitional cell hyperplasia of papilla