

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

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Involvement with TBA Studies

- Member of Pathology Working Group
 - Hard et al., Reg. Toxicol. Pharmacol., 59: 430-6, 2011
- Critique regarding chronic progressive nephropathy (CPN)
 - Hard et al., Toxicol. Sci., 132: 268-75, 2013
 - Hard et al., Crit. Rev. Toxicol., 39: 332-46, 2009
- Presentation to IRIS review of TBA, June, 2016
 - Recommended reviewer by National Academy of Sciences

TBA Pathology

- IRIS staff strongly encouraged by presenters at 2016 review to seek pathology expertise
- No pathologist on IRIS team
- Pathology expertise not listed as area of expertise needed for SAB
- No pathologist on SAB

α_{2u} -Globulin Nephropathy and Chronic Progressive Nephropathy (CPN)

- Both are defined disease entities
- Both are not relevant to humans

Chronic Progressive Nephropathy

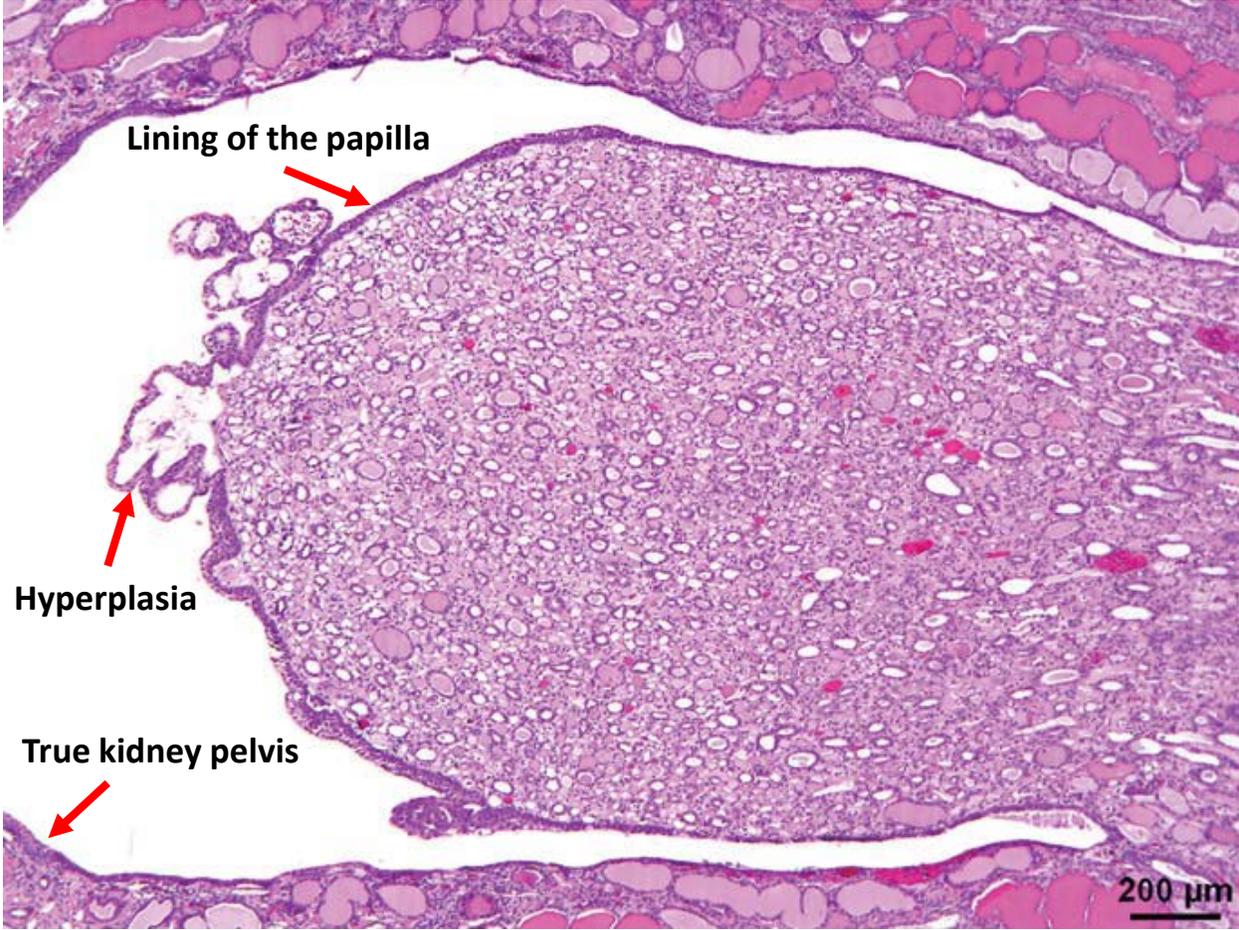
Features

Microscopic:	Tubular basophilia Nuclear crowding Thickened basement membrane Hyaline casts Tubular atrophy Tubular dilatation Focal glomerular sclerosis Glomerular atrophy Inflammatory infiltrate Interstitial fibrosis Transitional cell hyperplasia
Macroscopic:	Increased kidney weight
Clinical chemistry:	Increased BUN, creatinine, cholesterol
Biology:	Cell loss and regenerative tubular proliferation

Transitional Cell Hyperplasia

- Two types:
 - True urothelial hyperplasia of kidney pelvis
 - Usually associated with urothelial hyperplasia of urinary bladder
 - Hyperplasia of lining of renal papilla
 - Not truly urothelial
 - Unique to CPN (late stage)
 - Stated as part of CPN in NTP report on TBA (p. 56)
- With TBA and ETBE, only hyperplasia of lining of renal papilla

Hyperplasia of Lining of Renal Papilla



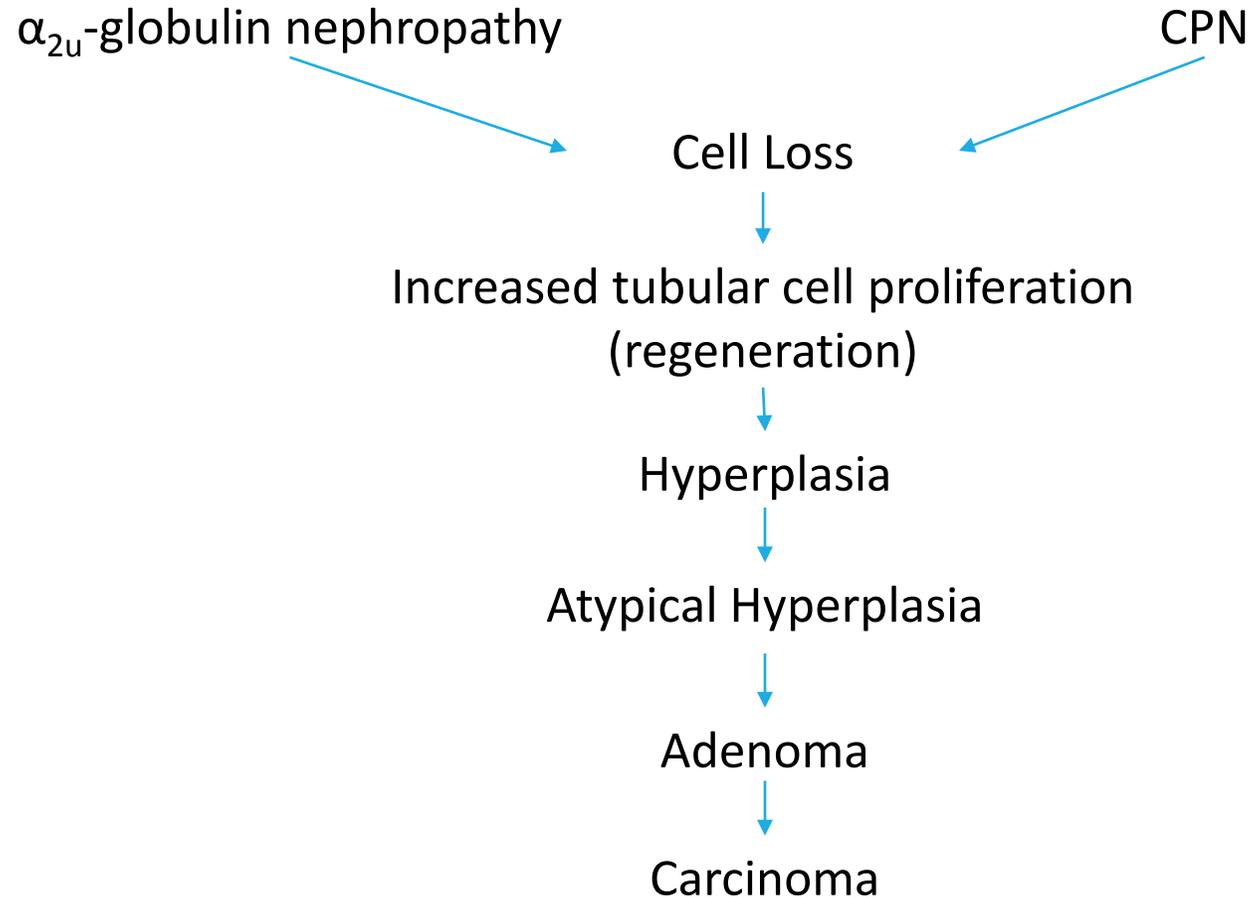
Statistical Analysis of Individual Components of CPN Are Inappropriate

- Numerator inaccurate
 - Pathologist does not always list every component of CPN in diagnostic list; combined as CPN
- Denominator inaccurate
 - Transitional cell hyperplasia and inflammation only occur in higher grade, late stages of CPN
 - Cannot use all animals with CPN as denominator
 - Nearly all F344 male rats will have at least early CPN by 20 weeks of age
- Hyperplasia of lining of renal papilla only occurs in rats with CPN and not seen in humans

CPN: Males and Females

- Males develop CPN earlier and more frequently
- Average CPN grade at end of two year study does not take into account length of time at higher stages or number of animals with end stage kidney disease
- “Transitional” cell hyperplasia and inflammation occur at later stages (high grades)
- Tumors occur mostly in CPN end stage kidneys (Grade 4/4)
 - Much more common in males than females

Mode of Action for TBA-related Kidney Tumors



Conclusion

- All findings in kidneys in TBA studies are due to α_{2u} -globulin nephropathy , chronic progressive nephropathy and cortico-medullary calcification
- None of these entities are relevant to humans
- Individual components cannot be separated for risk assessment purposes.