



NTP

National Toxicology Program

Longitudinal Residual Evaluations for Identifying Uterine Proliferative Lesions

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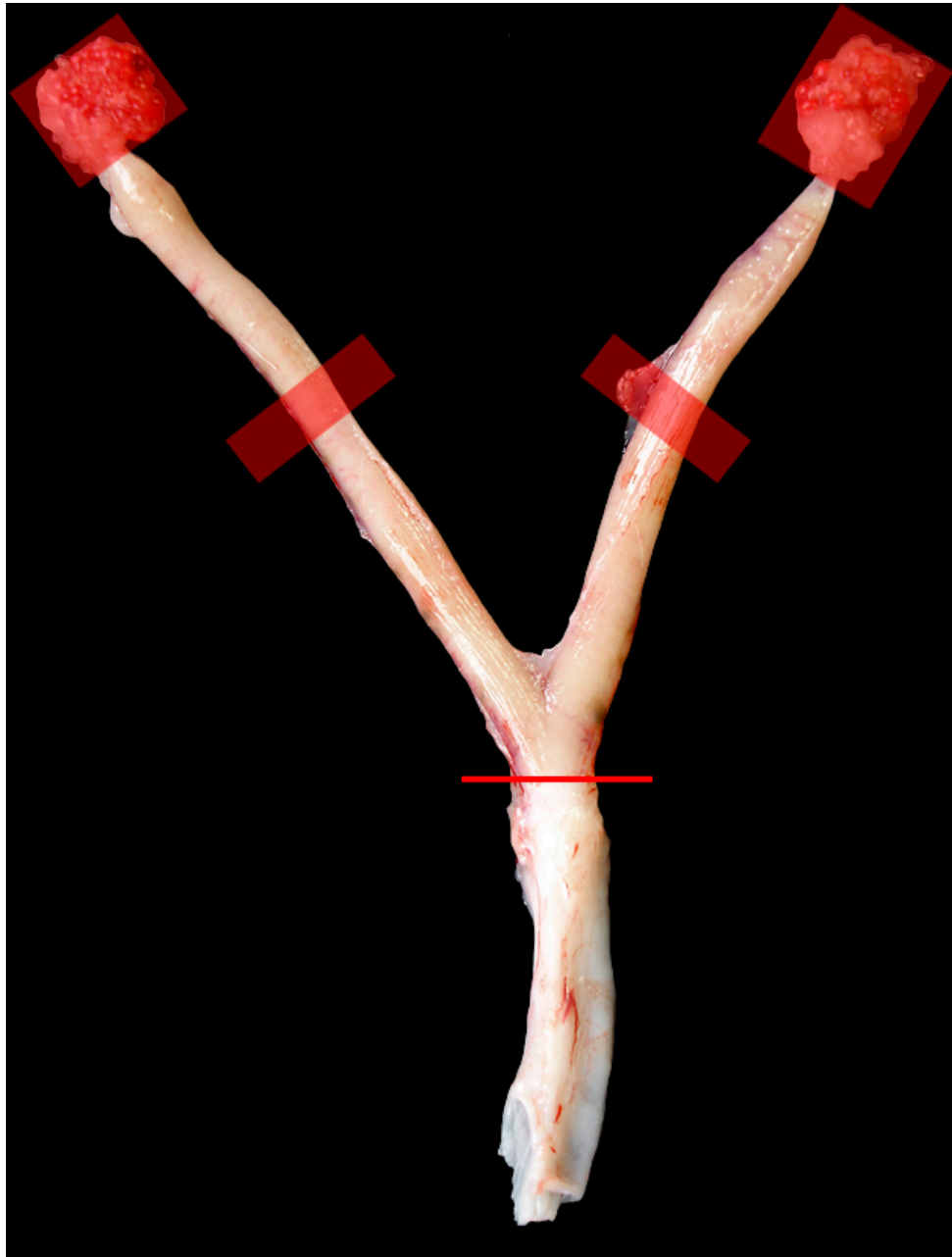


Current and Prior NTP Studies that have Used the Uterine Longitudinal Sectioning Protocol

- Tetrabromobisphenol A
- Cimstar
- Green Tea Extract
- Indole-3-Carbinol
- DE-71
- 2,3 Butanedione

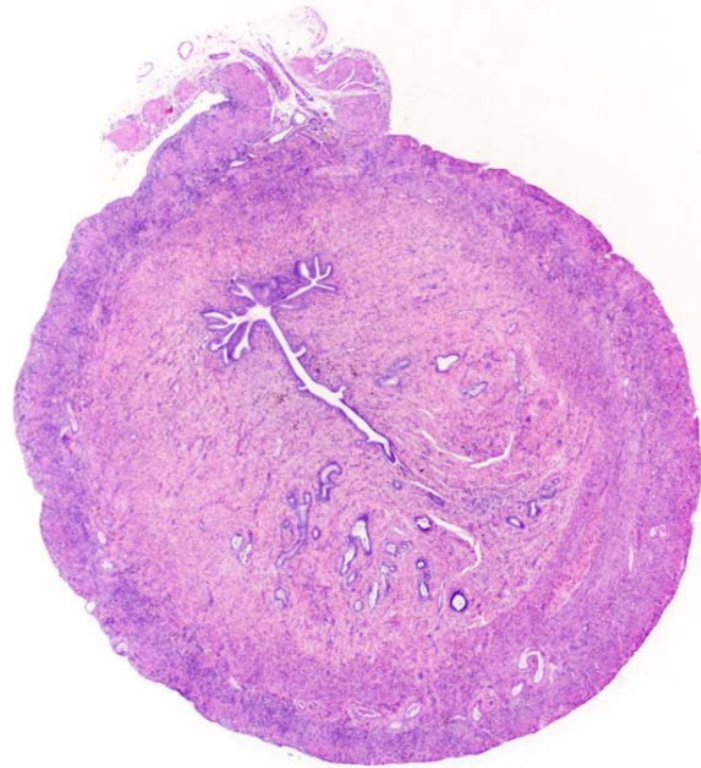
Original Transverse Versus Residual Longitudinal Uterine Reviews

- Original transverse tissue review
 - Transverse section through each uterine horn
 - Cervix/vagina not processed, unless gross lesions
- Residual longitudinal tissue review
 - Remaining formalin fixed cervix, vagina, and uterine remnants were sectioned longitudinally
- Original rationale for residual longitudinal tissue review came from the tetrabromobisphenol A study
 - To determine the primary location for adenocarcinomas in the cervix and vagina
 - To review all the cervixes for hyperplasia/fibrosis

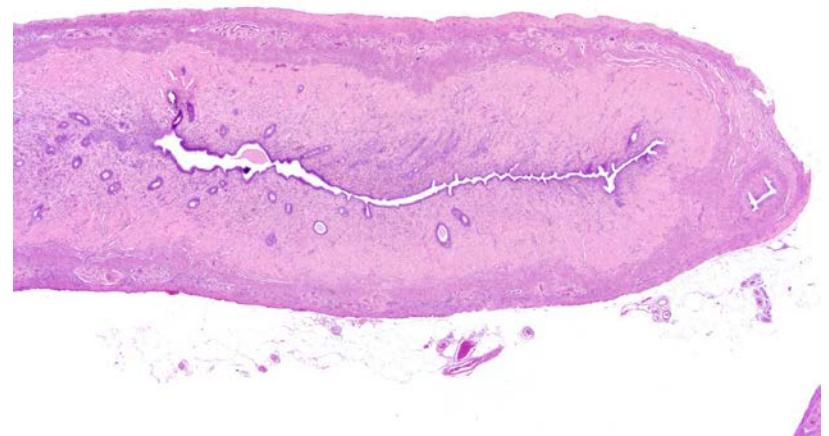
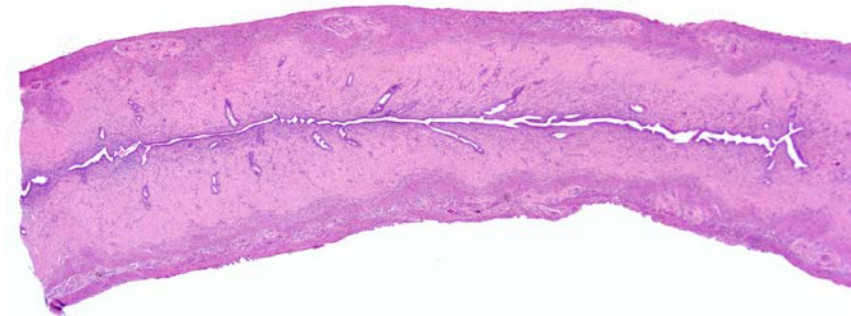


- Gross image of normal female rat reproductive organs
- Ovaries (red boxes) are attached
- Thick red horizontal lines show where a transverse cut is made through the uterine horns in the original review

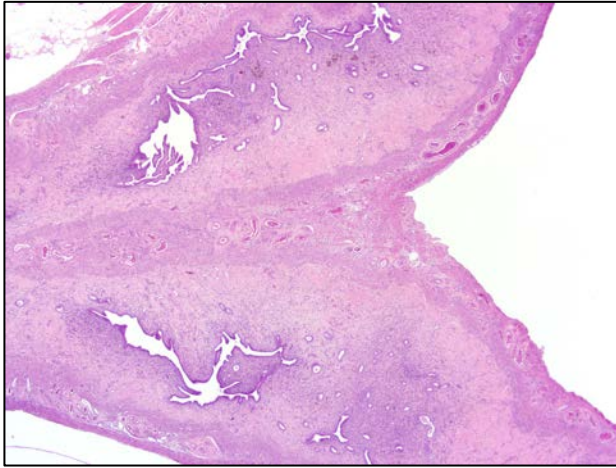
Original Review: Transverse Section From Each Uterine Horn



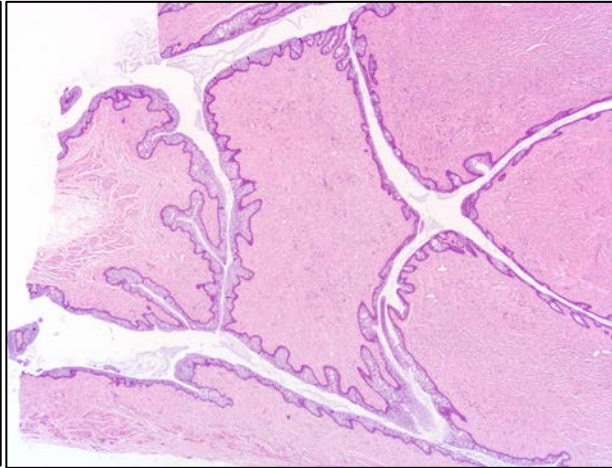
Longitudinal Sections of Left and Right Uterine Horns



Additional Sections of Longitudinal Tissue



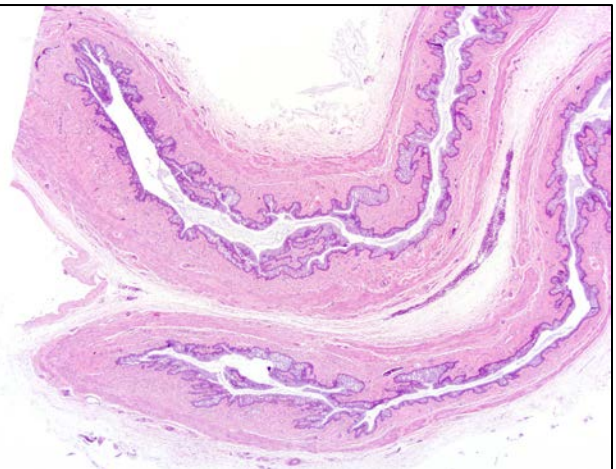
Uterus Body



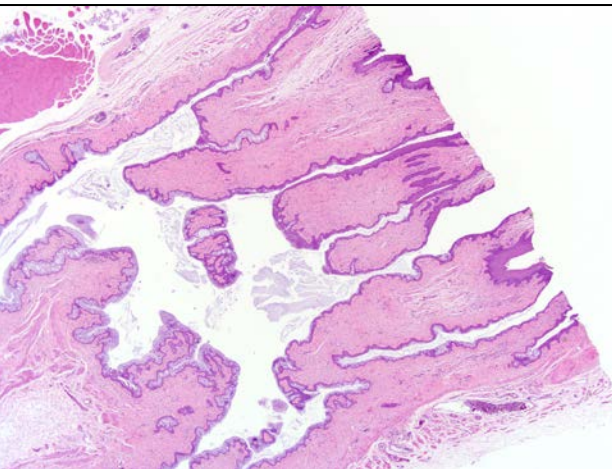
Distal Cervix



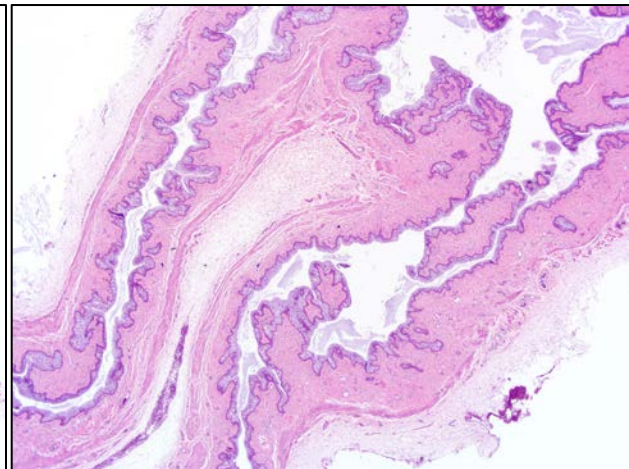
Proximal Cervix



Distal Vagina

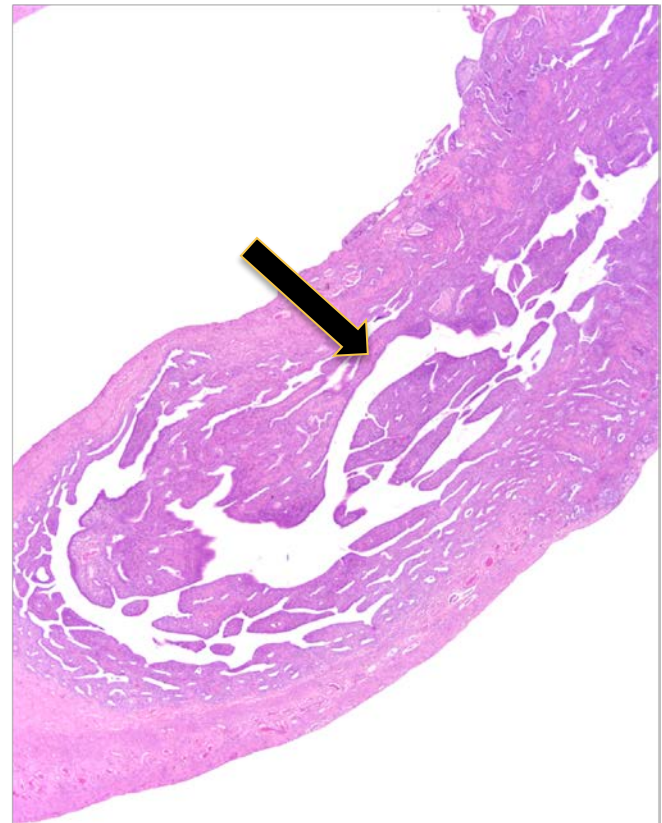
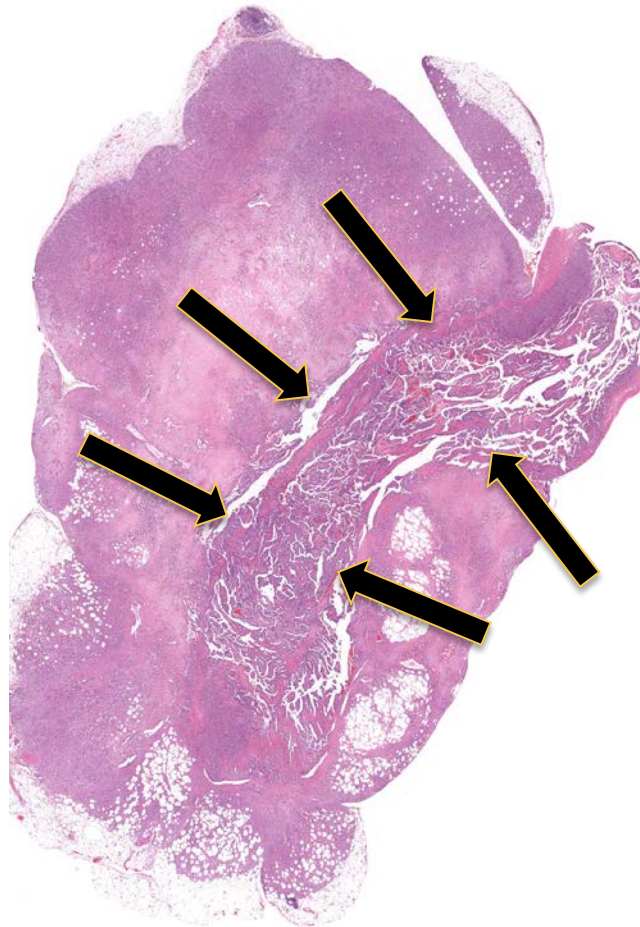


Proximal Vagina



Vagina/Cervix Junction

**Uterus on left shows a large expansive adenocarcinoma that was detected grossly.
Uterus on right also has an adenocarcinoma, but it was not detected grossly.**



Tetrabromobisphenol A Study Data

Tumor	0mg/kg	250mg/kg	500mg/kg	1000mg/kg
ORIGINAL TRANSVERSE REVIEW				
Adenoma, Adenocarcinoma, or Malignant Mixed Müllerian Tumor	3**	7	11*	13**
RESIDUAL LONGITUDINAL REVIEW				
Adenoma, Adenocarcinoma, or Malignant Mixed Müllerian Tumor	6**	10	16**	16**
Atypical Hyperplasia	2	13**	11**	13**
COMBINED ORIGINAL TRANSVERSE AND RESIDUAL LONGITUDINAL REVIEWS				
Adenoma, Adenocarcinoma, or Malignant Mixed Müllerian Tumor	6**	11	16**	19**
Atypical Hyperplasia	2	13**	11**	13**

* Positive trend test or significantly different ($p \leq .05$) from the control group by Poly 3 test

** Positive trend test or significantly different ($p \leq .01$) from the control group by Poly 3 test

Summary

- Residual longitudinal sectioning
 - Revealed additional uterine tumors, pre-neoplastic lesions, and non-neoplastic lesions in all groups
 - Was not included in the historical control data
 - Provided accurate diagnoses for some non-neoplastic lesions
 - Example: uterine dilatation due to cystic endometrial hyperplasia or uterine polyp
 - Determined primary site of invasive tumors
 - Cervix, vagina, uterus
 - Avoided misinterpretation of gross lesion incidences
 - Example: Cervical lesions
- Has been incorporated as standard protocol for NTP subchronic and chronic studies