

Use of Retrospective Pathology Peer Review and Pathology Working Groups to Address Critical Scientific and Regulatory Issues Sponsored by IATP, IFSTP, STP and STP-I



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Experimental Pathology Laboratories, Inc.



November 2, 2014, Bangalore, India

What is a Pathology Working Group (PWG)?



- Panel of independent expert pathologists assembled to review a specific question concerning study results
- Members selected from academia, private consultants, government, and industry
- May include Veterinary, Medical and/or Experimental Pathologists
- PWG participants selected based on their experience in toxicologic pathology and expertise with the target organ

What is the purpose of a PWG?



- Provide an independent assessment to address specific questions concerning study results
- The PWG does not review the entire study
- Review limited to specific findings or toxicologic end points
- Prospective pathology peer review and data audits used to provide a detailed review of study data

When should a PWG review be considered?



- Resolve differences between the Study and Peer Review Pathologist following routine histopathology peer review
- Address questions concerning data in final study reports
- Address issues concerning results published in peer reviewed journals
- Address questions that are of concern by regulatory agencies
- Comparison of results of multiple studies that may have been conducted and evaluated by different laboratories and/or different pathologists

Is a PWG review of study data required by regulatory agencies?



- Generally not required for data submitted to regulatory agencies
- EPA Pesticide Regulation (PR) Notice 94-5 is the only regulatory requirement for a PWG review
 - For any target tissue being reevaluated, all slides containing that tissue in all dose groups, as well as controls, must be re-examined by a peer review pathologist.
- May be required on a study-by-study basis by other regulatory agencies

What is the role of the Peer Review Pathologist?



- Non-routine retrospective review of the target organ tissue(s) for specific previously identified endpoints
- Evaluate the study pathologist's findings for consistency and accuracy
- Identify all lesions that are relevant to the issue being addressed, including “borderline lesions” that may otherwise not be selected for the PWG review

What is the role of the PWG Chairperson?



- Chairperson is generally not a voting participant of the PWG
- Must thoroughly understand the issue in question
- Reviews all relevant data and study results
- Responsible for the organization and conduct of the PWG
- Selects and prepares materials to be reviewed by the PWG
- Records PWG consensus findings
- Serves as the author of a detailed pathology report which includes the PWG findings and conclusions

How are slides selected for examination by the PWG?



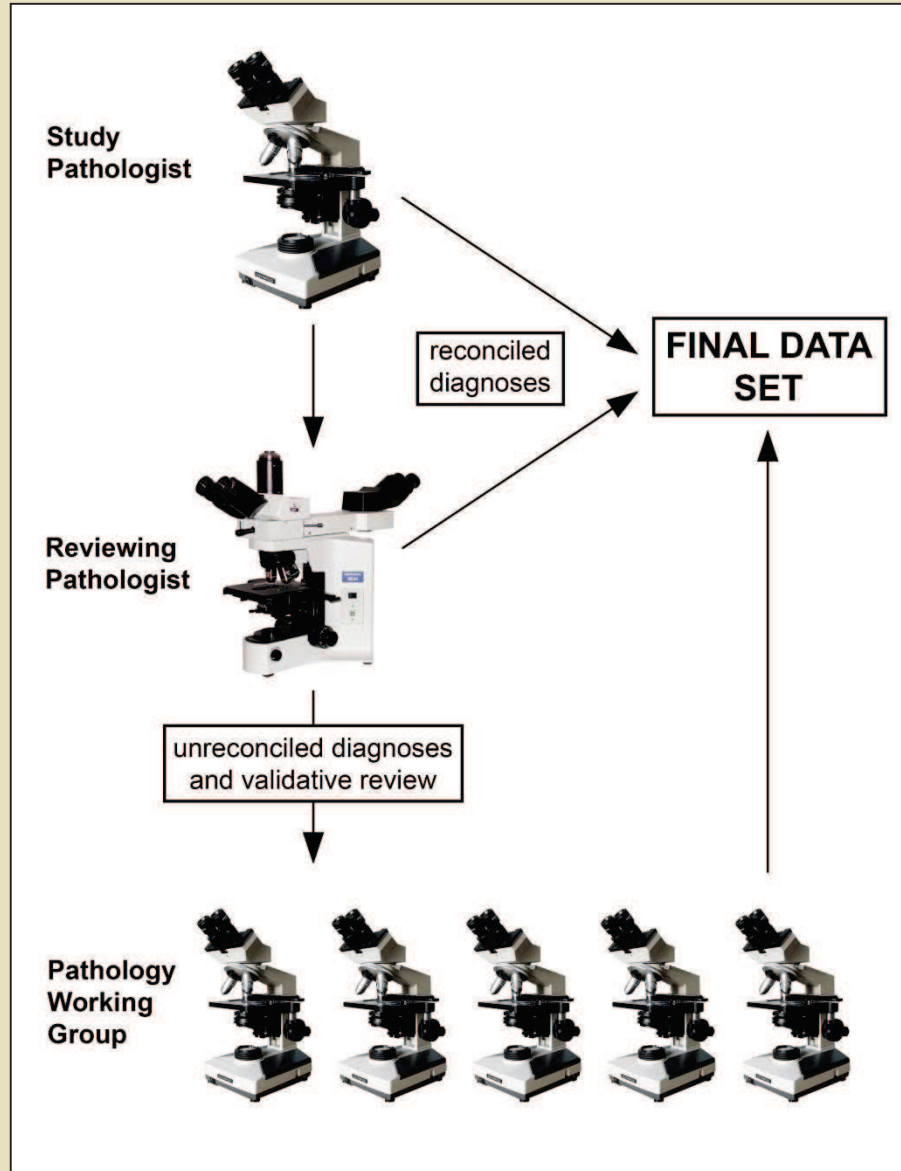
- The PWG examines, **as a minimum**, all slides with significant differences in diagnoses between the study and peer review pathologists (EPA PR Notice 94-5)
- Slides necessary to address the issue in question are selected for the PWG review by the chairperson
 - All slides with the diagnoses to be reviewed that were recorded by either the study or peer review pathologist
 - For example: all liver tumors in all animals
- In some instances, all target organs are examined by the PWG
 - For example: all sections of kidney from male rats to resolve the relationship of renal tumors to CPN or renal toxicity

How is the PWG review performed?



- PWG examines coded slides without knowledge of treatment group or previous diagnoses
- Each panel member records his/her diagnoses on worksheets provided by the chairperson
- Each member of the panel voices their opinion (vote) concerning each diagnosis
- In instances where there is wide variance of opinions concerning a diagnosis, the panel discusses the lesion and a second vote may be necessary

Peer Review/PWG Process



How is the PWG review performed?



- A PWG consensus diagnosis is determined for each slide examined by majority vote
- The final consensus diagnosis of the PWG is recorded by the PWG chairperson
- After the chairperson records the final PWG diagnoses, the results are decoded and tabulated for evaluation
- No changes in diagnoses are allowed after the final PWG diagnoses have been decoded
- The PWG panel evaluates the results and provides conclusions

Example PWG Worksheet: Proliferative Hepatocellular Lesions



PATHOLOGY WORKING GROUP DIAGNOSES

CHEMICAL NAME: XXXXXXXXXXXX

STUDY IDENTIFICATION: XXXXXXXXXXXXXXXX

SPECIES: Mice

STRAIN: B6C3F1
LIVER

SEX: Male/Female



Code Number	Animal Number	# of Slides		Hepatocellular Carcinoma (S or M)	Hepatocellular Adenoma (S or M)	Eosinophilic Focus (i)	Hemangiosarcoma	Other/ Comments
1		2						
2		2						
3		2						
4		2						
5		2						
6		3						
7		2						
8		2						
9		2						
10		2						
11		3						
12		2						
13		2						
14		2						
15		2						

KEY: (S or M) - (Single or Multiple)

Pathology Working Group





Application to Pathology Working Groups to Address Findings Observed During the Drug Development Process

Use of PWG to Clarify Findings Leading to Mechanistic Studies



Table 3. Incidence of Proliferative Lesions Diagnosed by the Pathology Working Group (PWG) in Male Rats in the 24-Month Repeated Dose Oral Carcinogenicity Study in the Rat.

Dosage Group	Vehicle Control 0 mg/kg/day	Low 10 mg/kg/day	Medium 30 mg/kg/day	High 100 mg/kg/day
No. Animals	65	65	65	65
Tubule Carcinoma	0	0	1	5
Tubule Adenoma	0	0	1	9
Tubule Carcinoma or Adenoma	0	0	2	12

Table 4. Incidence of Proliferative Lesions Diagnosed by the Pathology Working Group (PWG) in Female Rats in the 24-Month Repeated Dose Oral Carcinogenicity Study in the Rat.

Dosage Group	Vehicle Control 0 mg/kg/day	Low 10 mg/kg/day	Medium 30 mg/kg/day	High 100 mg/kg/day
No. Animals	65	65	65	65
Tubule Carcinoma	0	0	0	3
Tubule Adenoma	0	0	0	6
Tubule Carcinoma or Adenoma	0	0	0	8

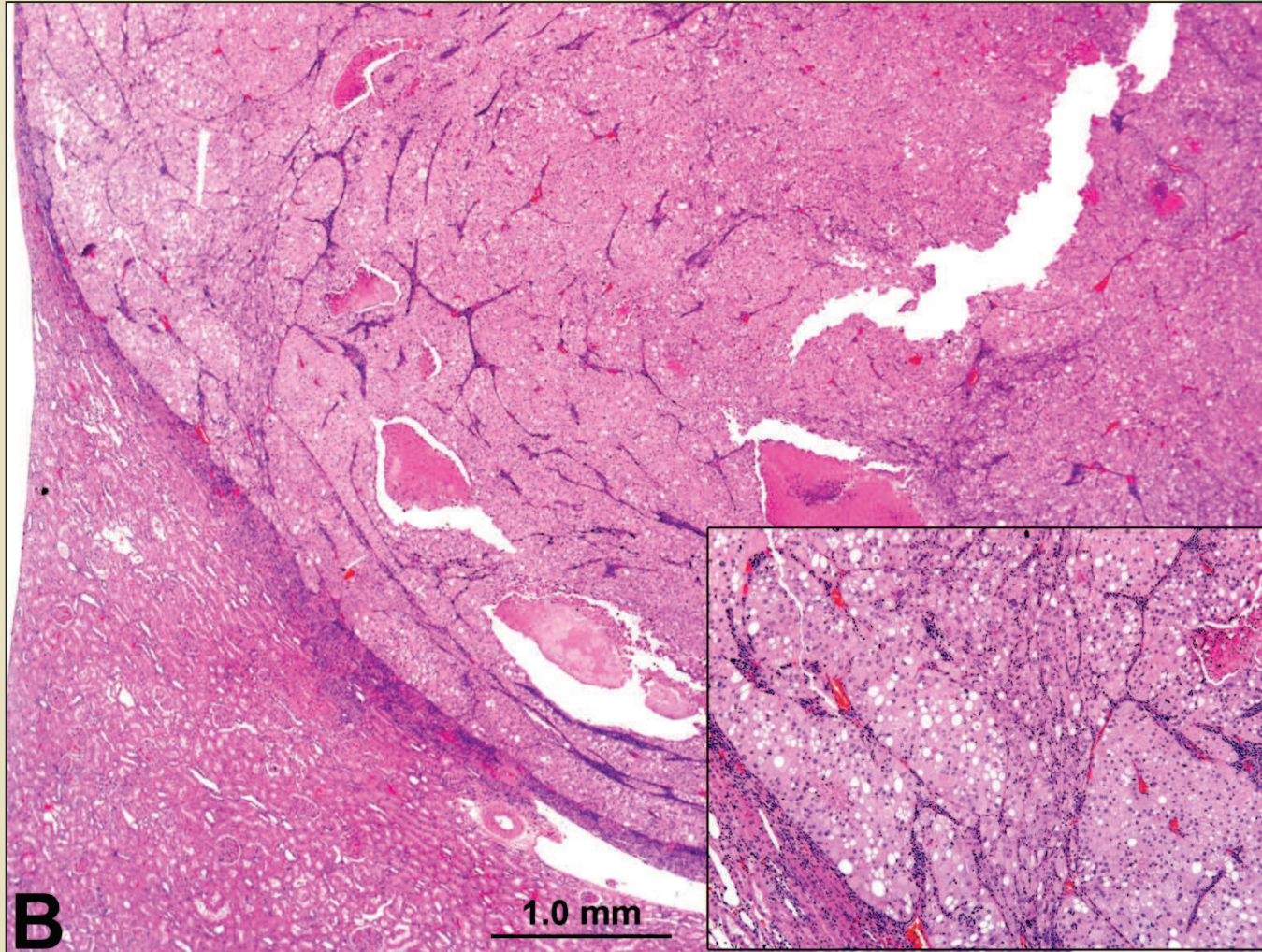
Carcinogenicity in rats of the SGLT2 inhibitor canagliflozin

Sandra De Jonghe^a, Jim Proctor^b, Petra Vinken^a, Bianca Feyen^a, Inneke Wynant^a, Dirk Marien^a, Helena Geys^a, Rao N.V.S. Mamidi^b, Mark D. Johnson^{b*}

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^bJanssen Research & Development, LLC, 1000 North 202 Street, Kenilworth, NJ 07033, United States

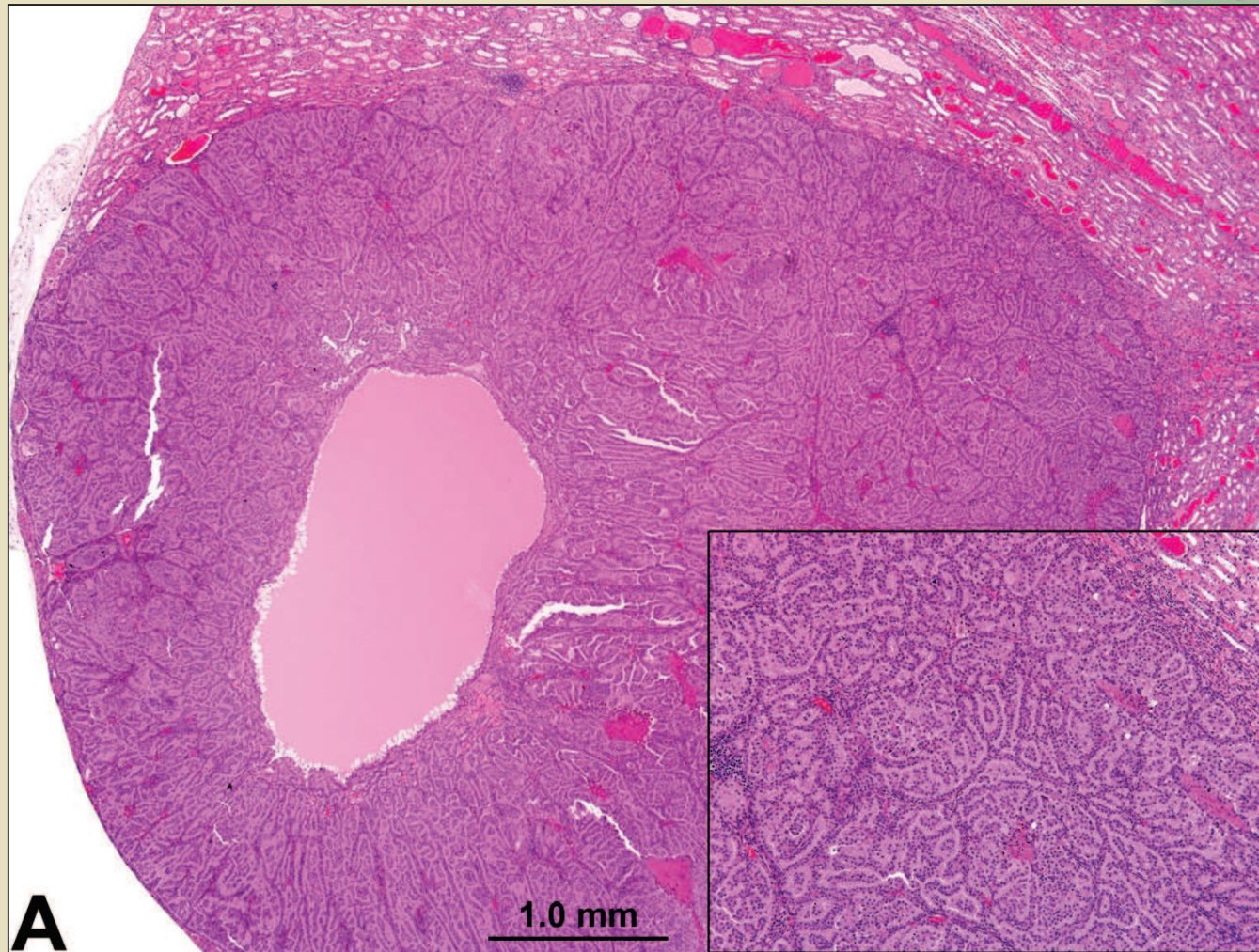


Amphophilic Vacuolated (AV) Tubular Cell Adenoma



Mid-dose Male

Basophilic Cell Type Tubular Cell Adenoma



A

1.0 mm

High Dose Male

Spontaneous Occurrence of a Distinctive Renal Tubule Tumor Phenotype in Rat Carcinogenicity Studies Conducted by the National Toxicology Program

GORDON C. HARD,¹ JOHN CURTIS SEELY,² GRACE E. KISSLING,³ AND LAURA J. BETZ⁴

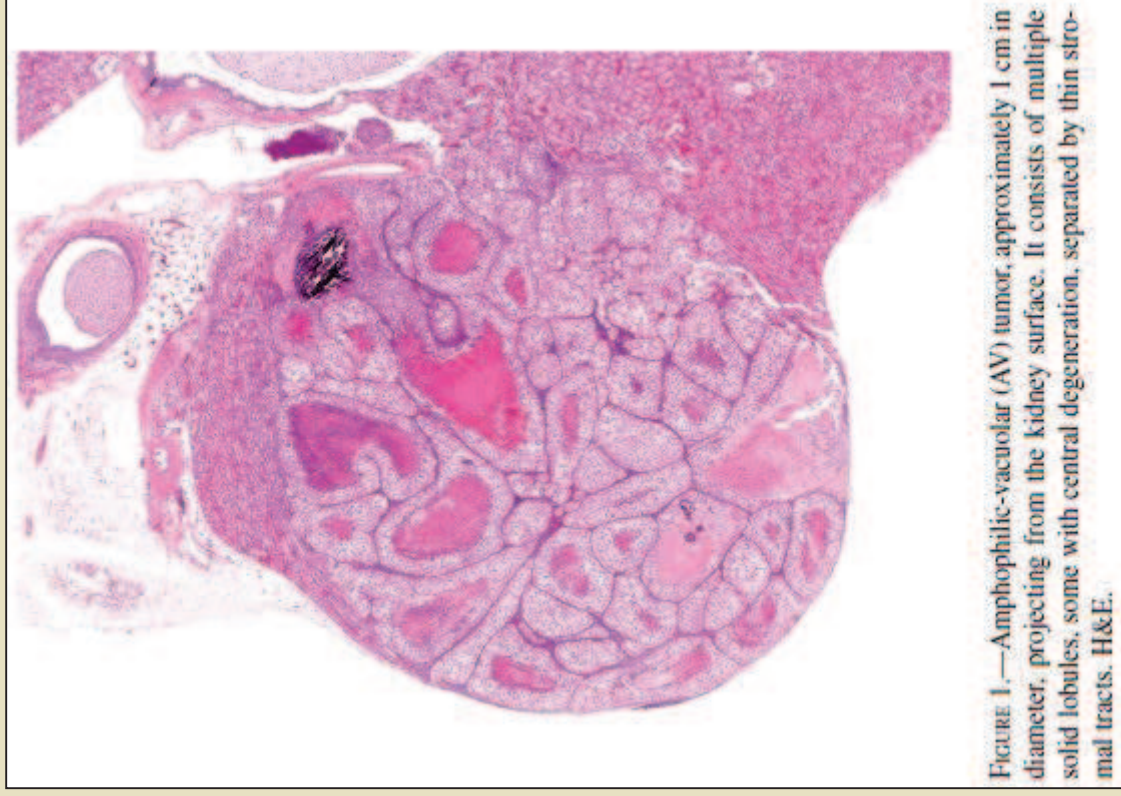


FIGURE 1.—Amphotericin B (AV) tumor, approximately 1 cm in diameter, projecting from the kidney surface. It consists of multiple solid lobules, some with central degeneration, separated by thin stromal tracts. H&E.



Sodium Glucose Co-Transport 2 (SGLT2) Inhibitor



- Developed for treatment of type 2 diabetes mellitus
- Increase urinary glucose excretion by blocking glucose reabsorption in the kidney mediated by SGLT2
- Decreased plasma glucose
- Carbohydrate malabsorption evidenced by inhibition of intestinal glucose uptake mediated by SGLT1
- Renal Tubule Tumors (RTT) in Sprague-Dawley male rats in 2-year carcinogenicity study

PWG Conclusions



Table 3. Incidence of Proliferative Lesions Diagnosed by the Pathology Working Group (PWG) in Male Rats in the 24-Month Repeated Dose Oral Carcinogenicity Study in the Rat.

Dosage Group	Vehicle Control 0 mg/kg/day	Low 10 mg/kg/day	Medium 30 mg/kg/day	High 100 mg/kg/day
No. Animals	65	65	65	65
Tubule Carcinoma	0	0	1	5
Tubule Adenoma	0	0	1	9
Tubule Carcinoma or Adenoma	0	0	2	12

- The two renal cell tumors in the mid-dose (30 mg/kg/day) male rats were considered not related to treatment due to their distinctive morphology which distinguished them from the tumors in the high dose group
- The two tumors were morphologically characteristic of a spontaneously occurring familial tumor that has been reported to occur in Sprague-Dawley rats

Mechanistic Study



Contents lists available at [ScienceDirect](#)

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint



Carbohydrate malabsorption mechanism for tumor formation in rats treated with the SGLT2 inhibitor canagliflozin



Rao N.V.S. Mamidi^a, Jim Proctor^a, Sandra De Jonghe^b, Bianca Feyen^b, Esther Moesen^b, Petra Vinken^b, Jing Ying Ma^c, Stewart Bryant^d, Sandra Snook^c, Calvert Louden^d, Godelieve Lammens^b, Kirk Ways^e, Michael F. Kelley^d, Mark D. Johnson^{a,*}

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- Glucose-free diet intervention effectively prevented glucose malabsorption



Application to Pathology Working Groups to Address Findings Reported in Peer Reviewed Published Literature

Dark Neurons vs. Pyknosis



Toxicol Sci. 2001 Aug;62(2):339-52.

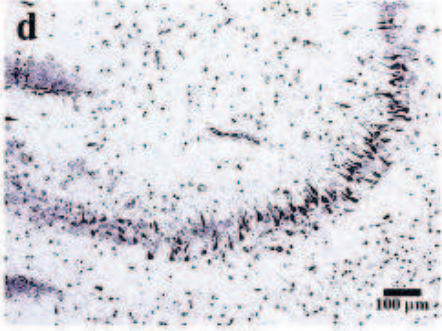
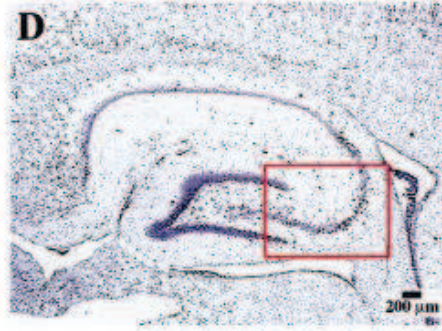
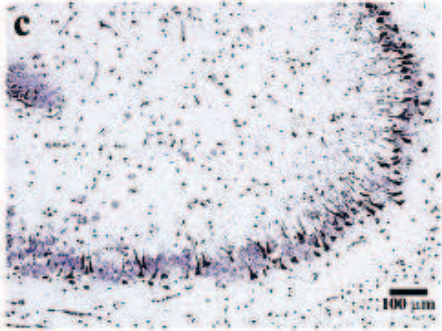
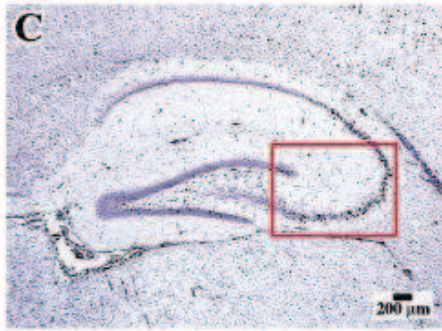
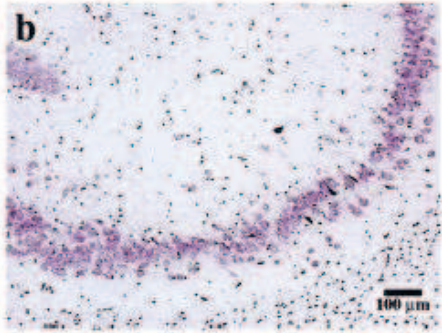
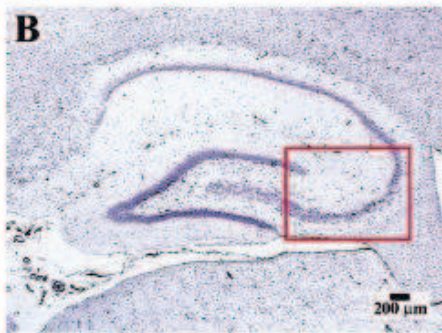
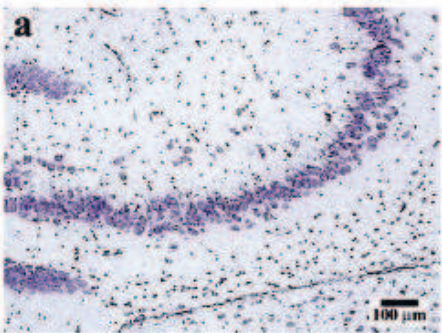
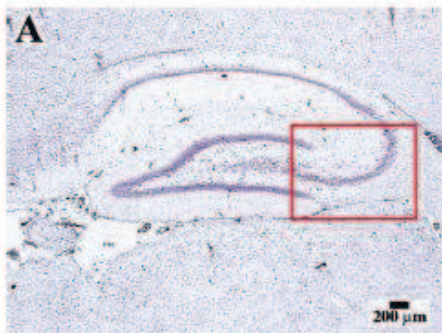
The effects of perinatal tebuconazole exposure on adult neurological, immunological, and reproductive function in rats.

Moser VC, Barone S Jr, Smialowicz RJ, Harris MW, Davis BJ, Overstreet D, Mauney M, Chapin RE.

Neurotoxicology Division and Environmental Toxicology Division, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, USA. moser.ginger@epa.gov

“Neuropathological evaluations revealed pyknotic cells across hippocampal cell fields in animals of all Tebuconazole treatment groups, with the highest incidence in the 20 and 60 mg/kg/day dose groups, coincident with cell loss within pyramidal cell layer of CA3-4 cell fields of the hippocampus and layer V of the neocortex.

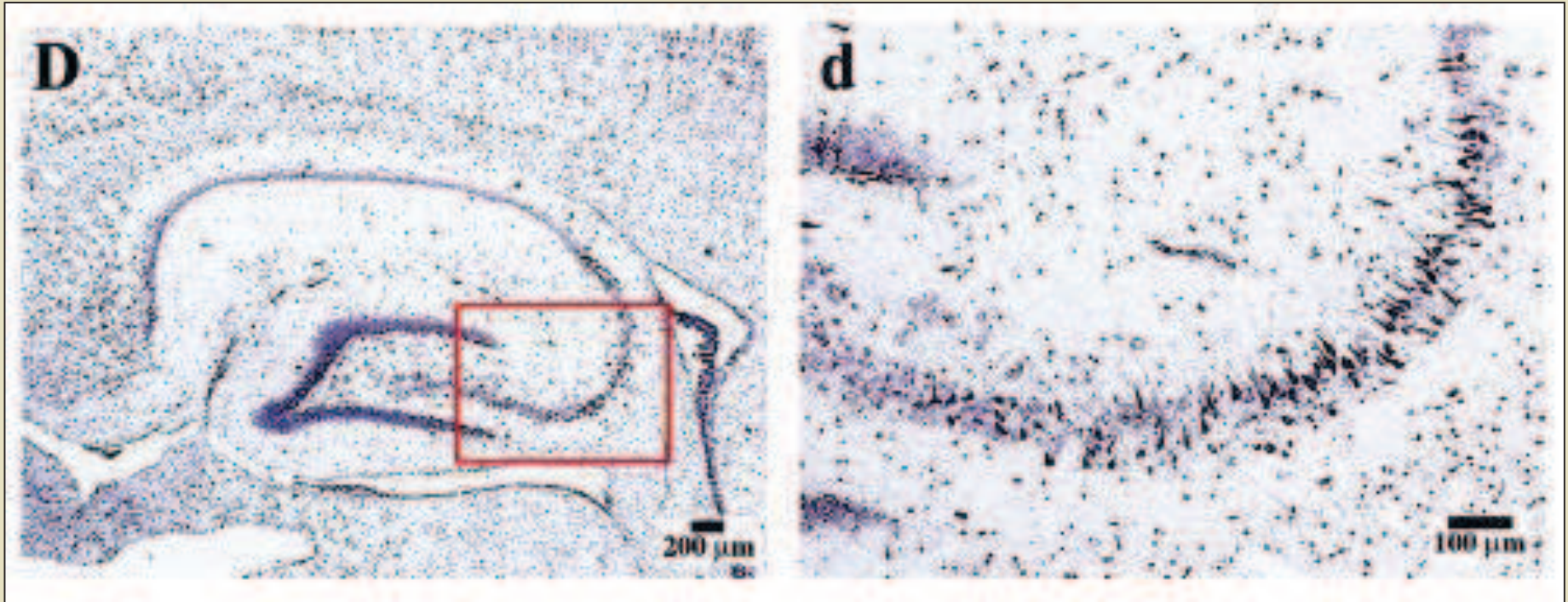
Thus, perinatal exposure to tebuconazole produced neurobehavioral deficits and neuropathology in rats, but did not alter immunological or reproductive function.”



TOXICOLOGICAL SCIENCES

62, 339–352 (2001)

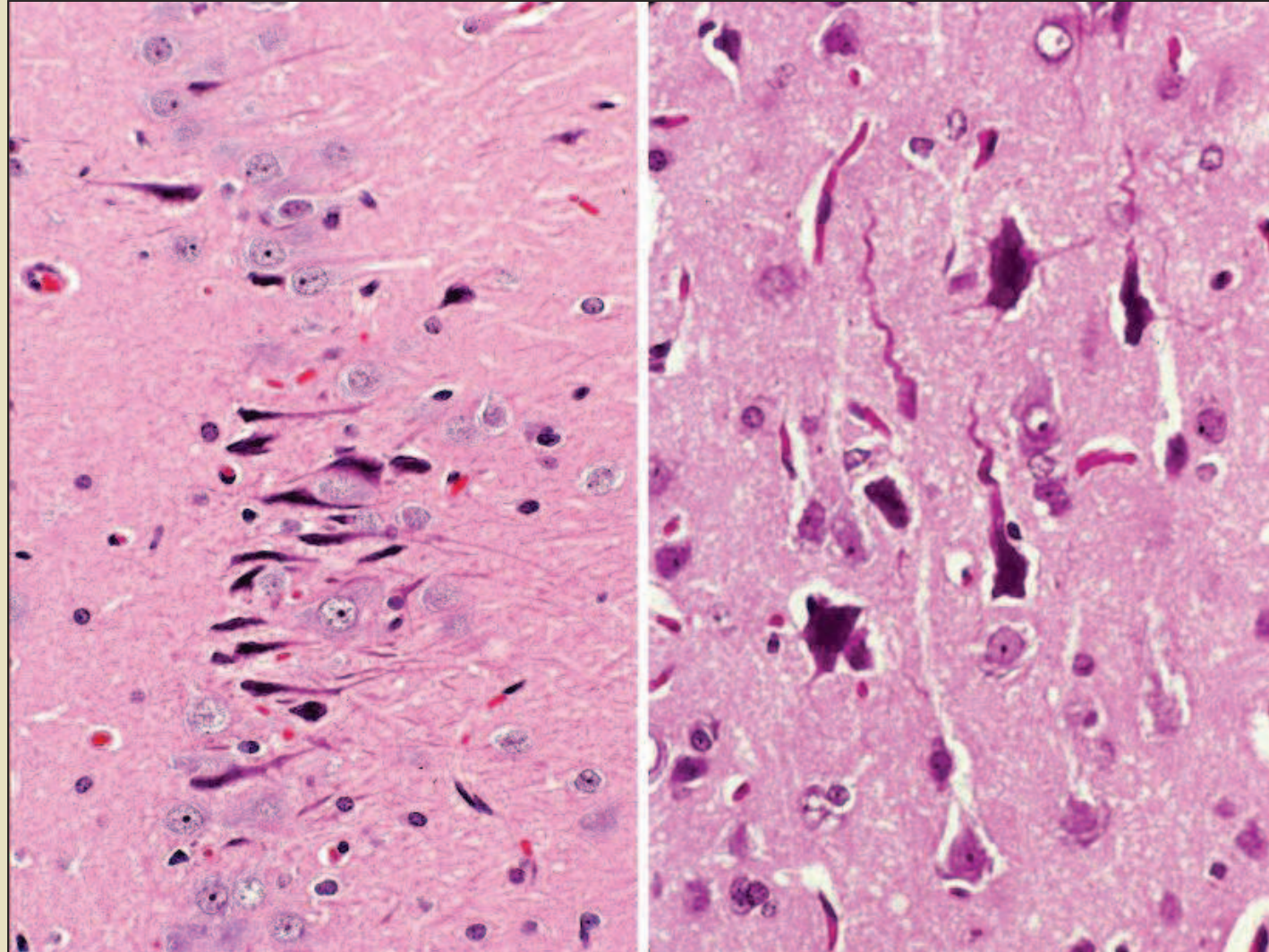




TOXICOLOGICAL SCIENCES 62, 339–352 (2001)

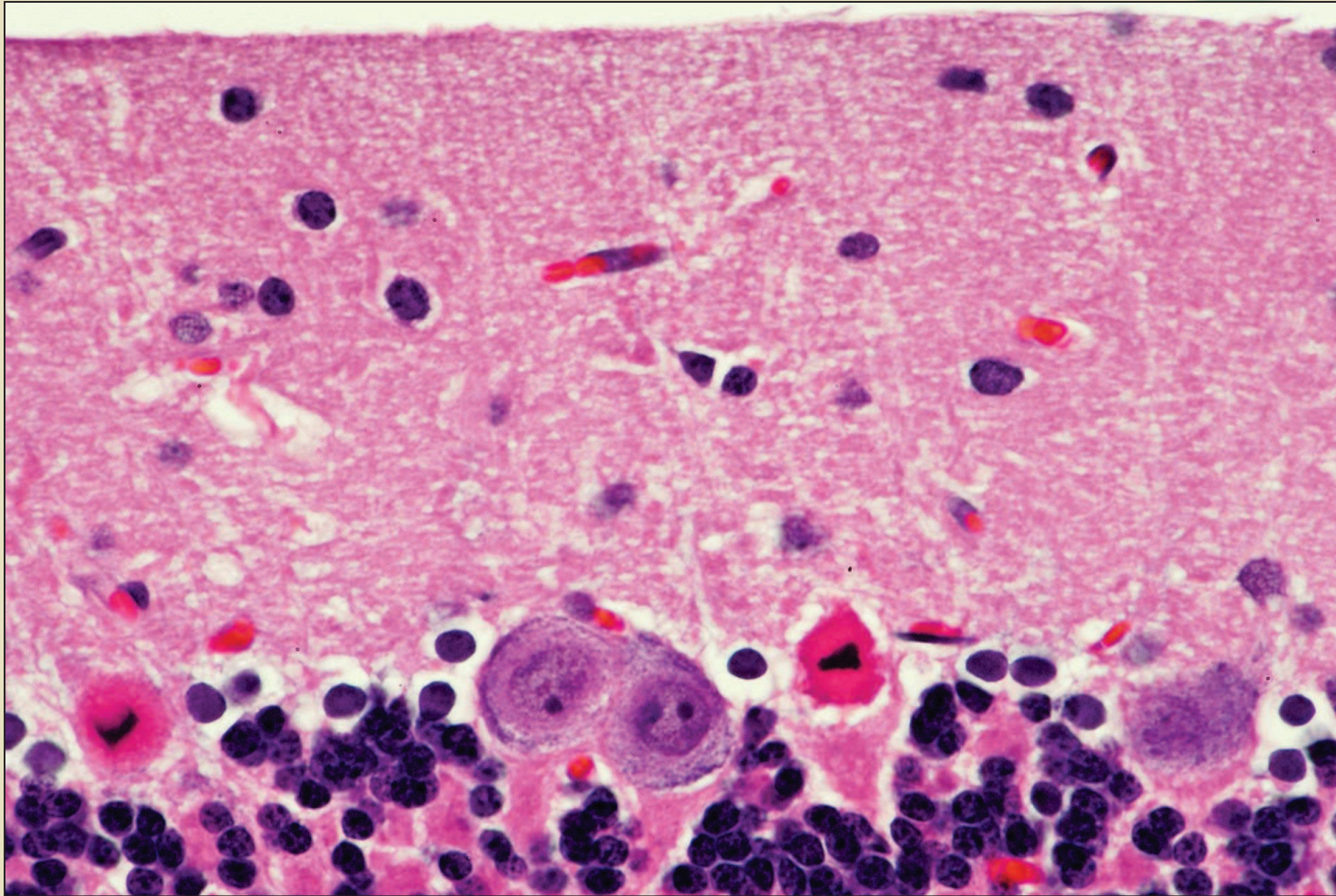
“Dark Neuron” Artifact

Most often the result of handling



Courtesy of R. Garman

Eosinophilic Neuron Acute Degeneration (“Red Dead Neurons”)



Courtesy of R. Garman

Barone & Moser (2004) wrote a retraction “Letter to the Editor”



The conclusion of the neuropathology peer review/PWG regarding the Moser et al. (2001) study was that “the dark neurons present in the brain sections were considered to be typical of those seen in association with handling artifact”.

TOXICOLOGICAL SCIENCES 77, 183 (2004)
DOI: 10.1093/toxsci/kfh036

LETTER TO THE EDITOR

To the Editor:

Our paper entitled “The Effects of Perinatal Tebuconazole Exposure on Adult Neurological, Immunological, and Reproductive Function in Rats” (Moser *et al.*, 2001) was part of a multidisciplinary project to evaluate long-term effects of developmental exposure to several different pesticides and to compare those effects across multiple forms of toxicity (neuro-, immuno-, and reproductive toxicity). We reported that tebuconazole produced impaired cognition, neuropathology, and altered organ weights, whereas immune and reproductive function were not affected. Questions arose regarding the finding of a treatment-related increase in the number of dark staining neurons and cell loss. To address these questions, we convened a group of expert neuropathologists to re-examine the histological sections of brain from this study. Following this re-examination, we concluded that the dark staining neurons were not pyknotic cells but were artifacts related to fixation and handling, and not a direct result of treatment.

Based on this new interpretation, we now withdraw all neuropathological conclusions in the paper, and their implications or relevance to any other findings. The neurobehavioral, immunological, and general toxicity findings of the paper stand unchanged.

This letter to the editor does not necessarily reflect EPA policy.

S. Barone, Jr.
V. C. Moser

Neurotoxicology Division
NHEERL/JORD
U.S. EPA
Research Triangle Park, NC 27711

REFERENCE

Moser, V. C., Barone, S. Jr., Smialowicz, R. J., Harris, M. W., Davis, B. J., Overstreet, D., Mauney, M., and Chapin, R. E. The Effects of Perinatal Tebuconazole Exposure on Adult Neurological, Immunological, and Reproductive Function in Rats. *Toxicol. Sci.* 62, 339–352.

Dark Neurons



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Available online at www.sciencedirect.com

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NeuroToxicology 27 (2006) 628–634

Commentary-Forum Position Paper

The return of the dark neuron. A histological artifact complicating contemporary neurotoxicologic evaluation

Bernard S. Jortner*

*Laboratory for Neurotoxicity Studies, Virginia-Maryland Regional College of Veterinary Medicine,
Virginia Tech, Blacksburg, VA 24061-0442, United States*

Received 22 December 2005; accepted 2 March 2006

Available online 22 March 2006

NeuroToxicology

Veterinary use of the drug diclofenac—used in the treatment of livestock—has been linked to the collapse of vulture populations throughout South Asia.



Inexpensive NSAID used to treat livestock with lameness or fever

Nature. 2004 Feb 12;427(6975):630-3. Epub 2004 Jan 28.

Diclofenac residues as the cause of vulture population decline in Pakistan.

Oaks JL¹, Gilbert M, Virani MZ, Watson RT, Meteyer CU, Rideout BA, Shivaprasad HL, Ahmed S, Chaudhry MJ, Arshad M, Mahmood S, Ali A, Khan AA.

A Drug Used for Cattle Is Said to Be Killing Vultures

By JAMES GORMAN
Published: January 29, 2004

Banned diclofenac still kills vultures

Raakhi Jagga : Ludhiana, Sun Aug 07 2011, 03:34 hrs



White-rumped Vulture, © J.C. Eames



Pathology Working Group Review of Histopathologic Specimens from Three Laboratory Studies of Diclofenac In Trout



Table 1: Summary of experimental designs and reported outcomes from four laboratory studies of diclofenac in trout

Study	Design	Diclofenac Conc. Tested (µg/L)	n per dose group (total n)	Fixation / Staining	Tissues Examined	Tissues with Exposure Related Findings	No Observed Effect Concentration (NOEC)	Organ with Lowest Observed Effect Concentration (LOEC)
Schwalger et al., 2004	1.8 y rainbow trout; 28 d exp.; no replicates	0, 1, 5, 20, 100, 500	10 (50)	Formalin / H&E, PAS (kidney)	Gills, Liver, Kidney, Spleen, Intestine	Gills, Kidney	1 µg/L	Gills, Kidney (5 µg/L)
Hoeger et al., 2006	18 m brown trout; 21 d exp.; no replicates	0, 0.5, 5, 50	6 (24)	Formalin / H&E; IHC (granulocytes, Thrombocytes, MHCII)	Gills, Liver, Head and Trunk Kidney, Spleen, Intestine	Gills, Liver, Trunk Kidney	0.5 µg/L	Liver (5 µg/L)
Mehinto et al., 2010	Juvenile (5 w +) female rainbow trout; 21 d exp.; 2 replicates	0, 0.5, 1, 5, 25	10 (50)	Boulin's / H&E	Gills, Liver, Kidney, Intestine	Kidney, Intestine	0.5 µg/L	Kidney, Intestine (1 µg/L)
Memmert et al., 2018	Juv. rainbow trout; 95 d exp. (33 d prehatch, 62 d posthatch); 4 replicates	0, 0.2, 10, 32, 100, 320, 1000	20 (140)	Davidson's / H&E; Azan; Heidenhain's (gills)	Gills, Liver, Kidney (whole fish sections)	Gills	320 µg/L	Gills (1000 µg/L)

Study example of findings in trout gills as determined by the study pathologist and the Pathology Working Group (PWG).



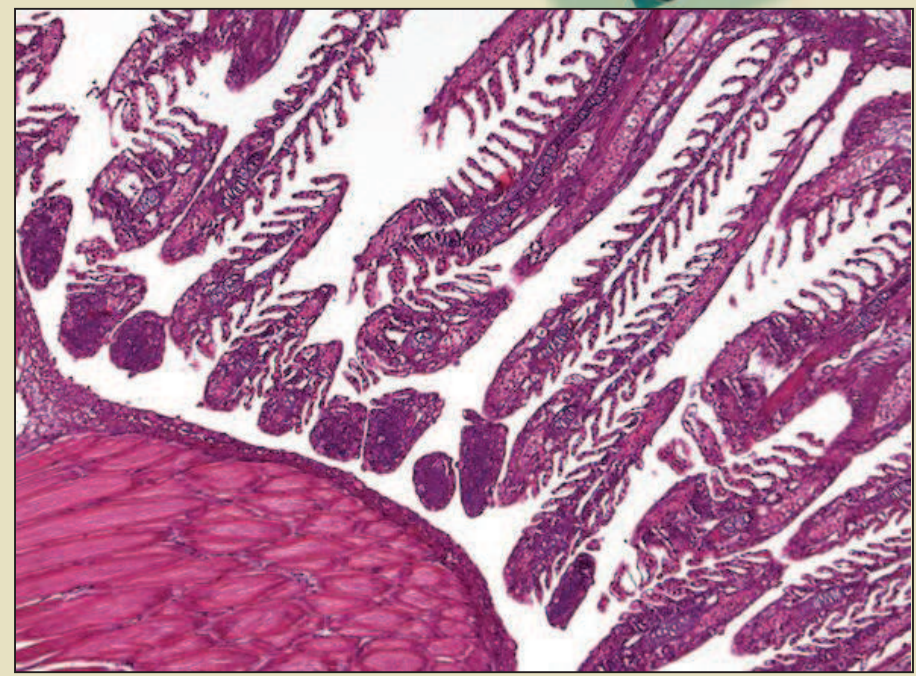
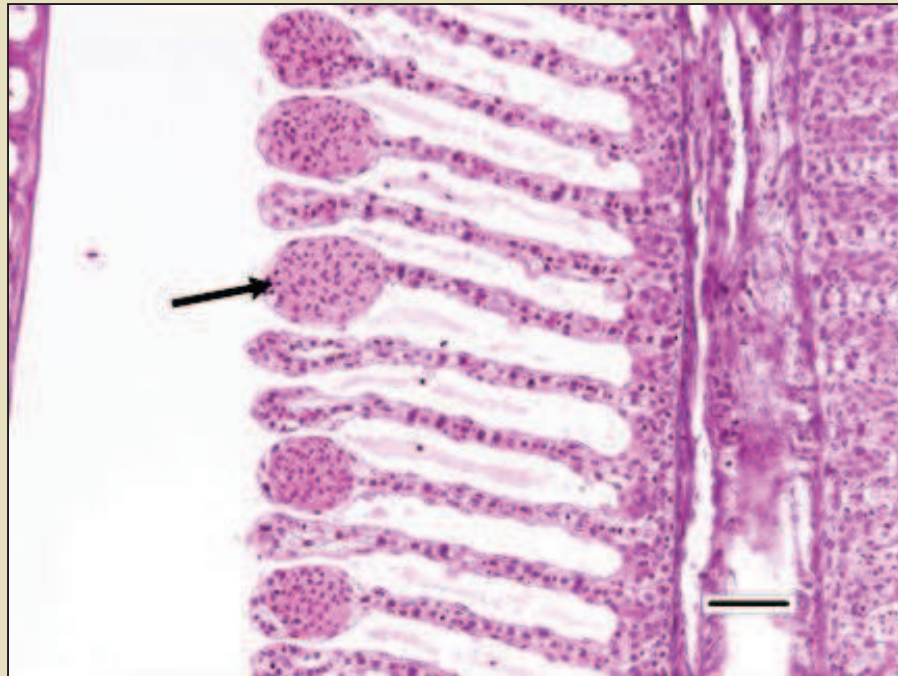
Background findings not reported in controls by study pathologist

	Study pathologist				PWG		
	0	0.5 (NOEC)	5 (LOEC)	50	0	0.5	5
Diclofenac concentration (µg/L)	0	0.5 (NOEC)	5 (LOEC)	50	0	0.5	5
n ^a	6	6	6	6	6	6	6
Lamellar clubbing	0	0	0	4	4	5	2
Lamellar Epithelial Hyperplasia	0	0	2	2	5	6	6
Mucous Cell Hyperplasia	0	0	1	0	0	1	2
Secondary Lamellar Fusion	0	0	1	2	4	4	4
Telangiectasis	0	5	2	4	2	6	2
Thickened Filament Tips	0	0	1	0	5	3	4

^aNumber of sections evaluated; ^bNumber of animals affected

Control, NOEC and LOEC examined by PWG

Trout gills, left: control fish with telangiectasis (not treatment-related), right: diclofenac-treated fish with thickened filament tips



Control fish with telangiectasis
(not treatment-related)

Diclofenac-treated fish with
thickened filament tips

- PWG confirmed increased thickening of gill filament tips at 1000 $\mu\text{g/L}$
- Other reported findings were not confirmed by the PWG in any of the studies

Reference: Aquatic Toxicology 2014



Aquatic Toxicology 146 (2014) 127–136

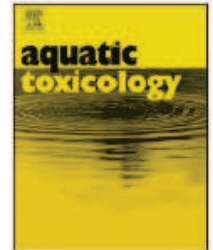


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Contents lists available at ScienceDirect

Aquatic Toxicology

journal homepage: www.elsevier.com/locate/aquatox



Pathology working group review of histopathologic specimens from three laboratory studies of diclofenac in trout[☆]



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Jerry F. Hardisty^e

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^c Centre for Fish and Wildlife Health, University of Bern, Bern, Switzerland

^d AnaPath GmbH, Oberbuchsitzen, Switzerland

^e Experimental Pathology Laboratories, Inc., Research Triangle Park, NC, USA



Application to Pathology Working Groups to Resolve Differences between the Study and Peer Review Pathologists

Issue Resolved by Peer Review and PWG



- Two-Year inhalation study with man-made fiber
- Study pathologist reported two mesotheliomas (one at 9 months –lowest exposed group; second at 24 months – highest exposure group)
- Sponsor's Reviewing Pathologist considered the two tumors to be malignant thymomas
- PWG confirmed that both tumors were Alveolar/Bronchiolar Carcinomas with unusual presentation

Mediastinal Tumors Resembling A/B Carcinomas in F344/N Rats

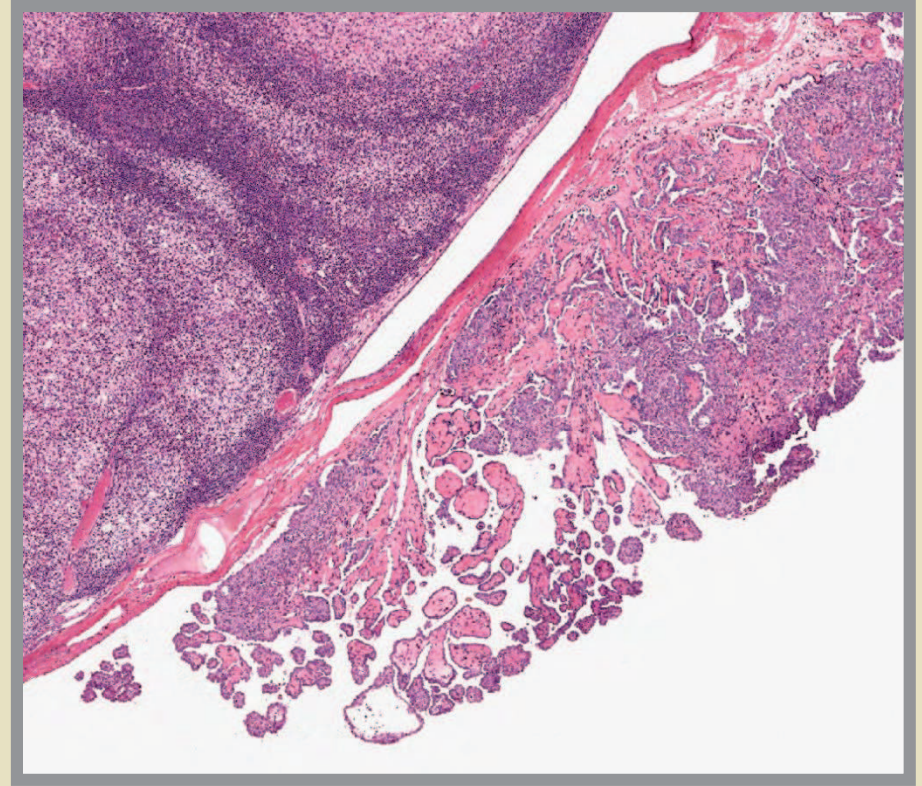
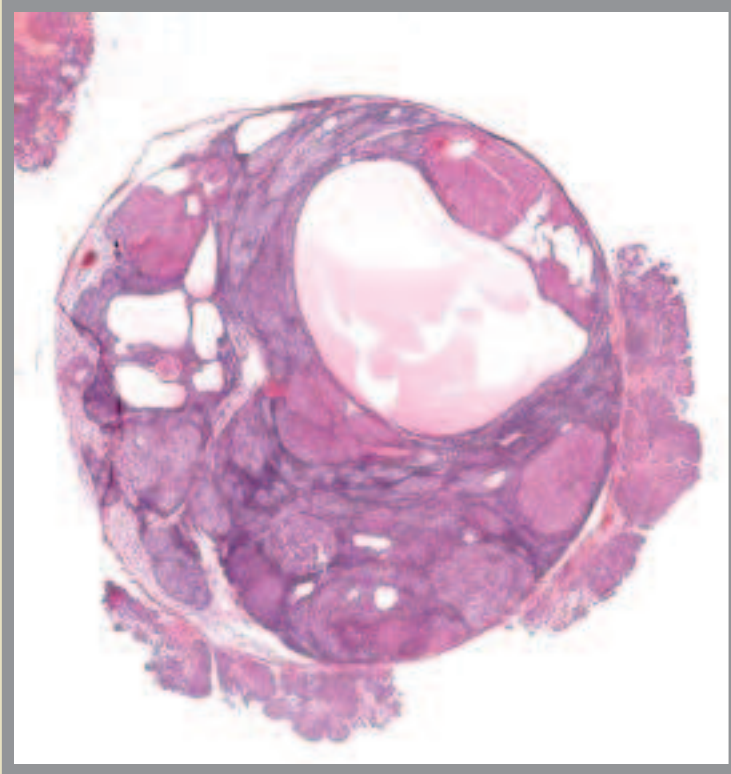


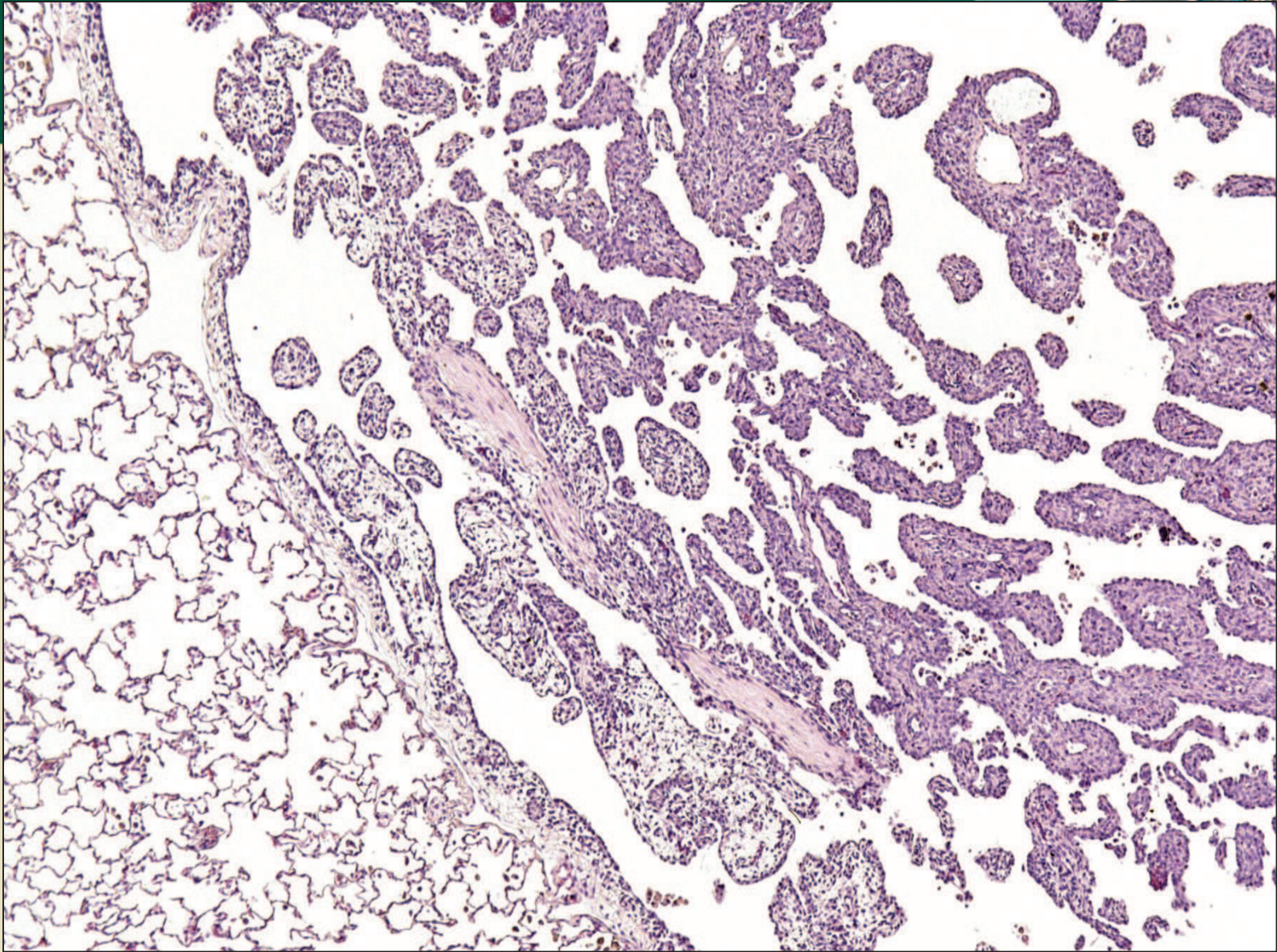
- Uncommon
- Totally or largely mediastinal
- Typical A/B carcinoma morphology
- Apparent alveolar macrophages are usually present
- Most diagnosed as A/B neoplasms, but some confused with mesotheliomas, or thymomas
- Becomes a diagnostic problem when there is some mesothelial reaction containing thin papillae lined by epithelial cells next to the main mass

Mesothelioma

- Rare in F344/N rats
- Grow along serosal surfaces
- Most common origin tunica vaginalis
- Rarely infiltrate the lung

Mesothelioma of Tunica Vaginalis in F344 Rats



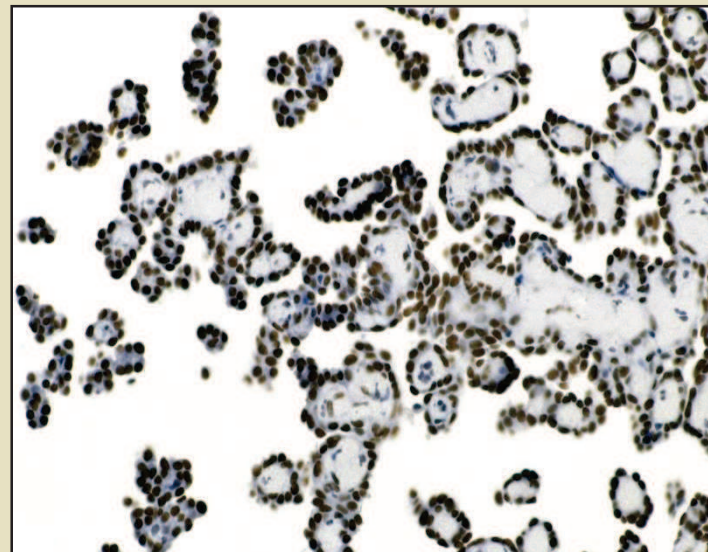


Pleural Epithelial Mesothelioma

Immunostains

- Nuclear Wilm's Tumor 1 (WT1) Susceptibility Gene Product – mesenchymal cell tumor suppressor gene, useful marker in humans to help differentiate mesotheliomas from epithelial lung tumors
- Surfactant Apoprotein A (SP-A) – useful epithelial marker
- CCSP (Clara Cell Secretory Protein) present in Clara in humans, rats, mice and other species

Mesothelioma with WT1 Stain



Incidences of Mediastinal A/B Carcinomas in Controls

- B6C3F1 Mice - None
- F344 Rats – 30/592 A/B carcinomas

Mesothelioma, Malignant Thymoma, or Alveolar/Bronchiolar Carcinoma



Toxicologic Pathology, 37: 351-358, 2009
Copyright © 2009 by The Author(s)
ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623309332988

Apparent Alveolar Bronchiolar Tumors Arising in the Mediastinum of F344 Rats

PAUL HOWROYD,^{1,2} NEIL ALLISON,^{1,3} JULIE F. FOLEY,⁴ AND JERRY HARDISTY¹

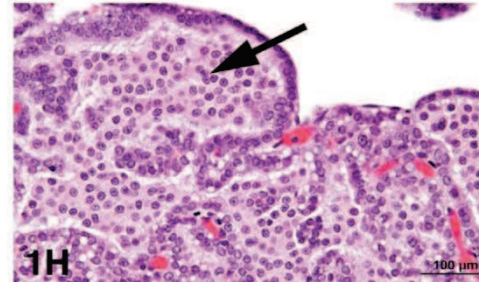
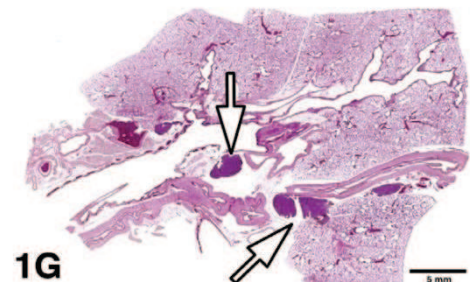
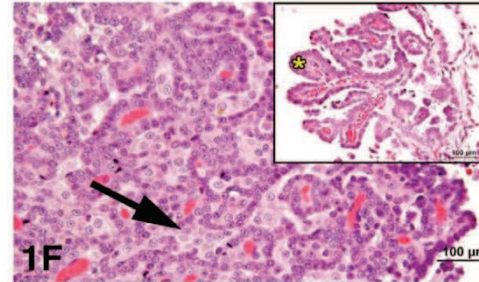
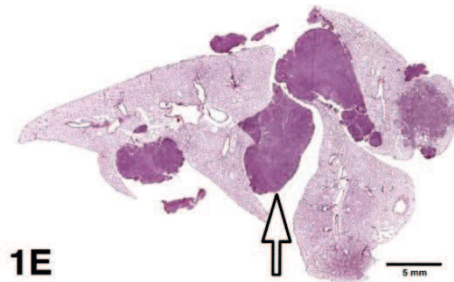
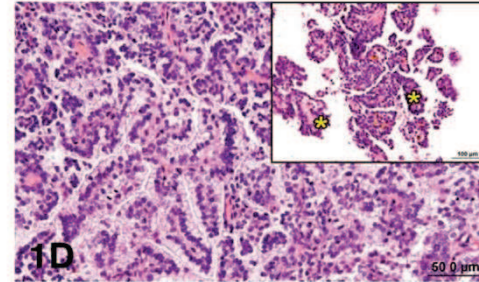
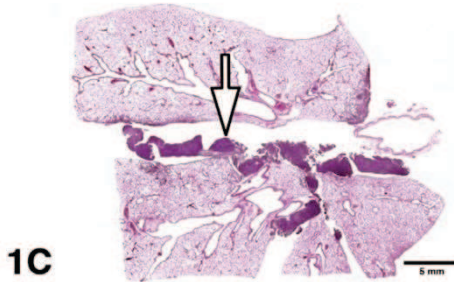
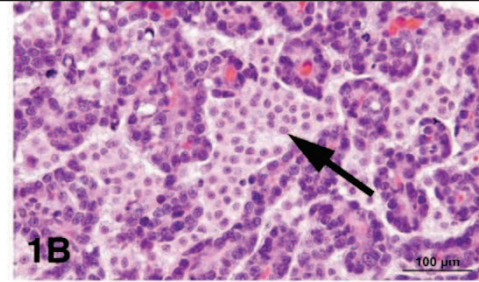
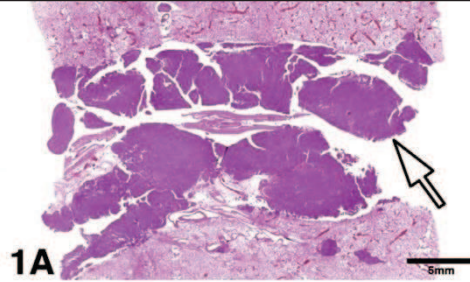
¹*Experimental Pathology Laboratories, Inc., Research Triangle Park, North Carolina, USA*

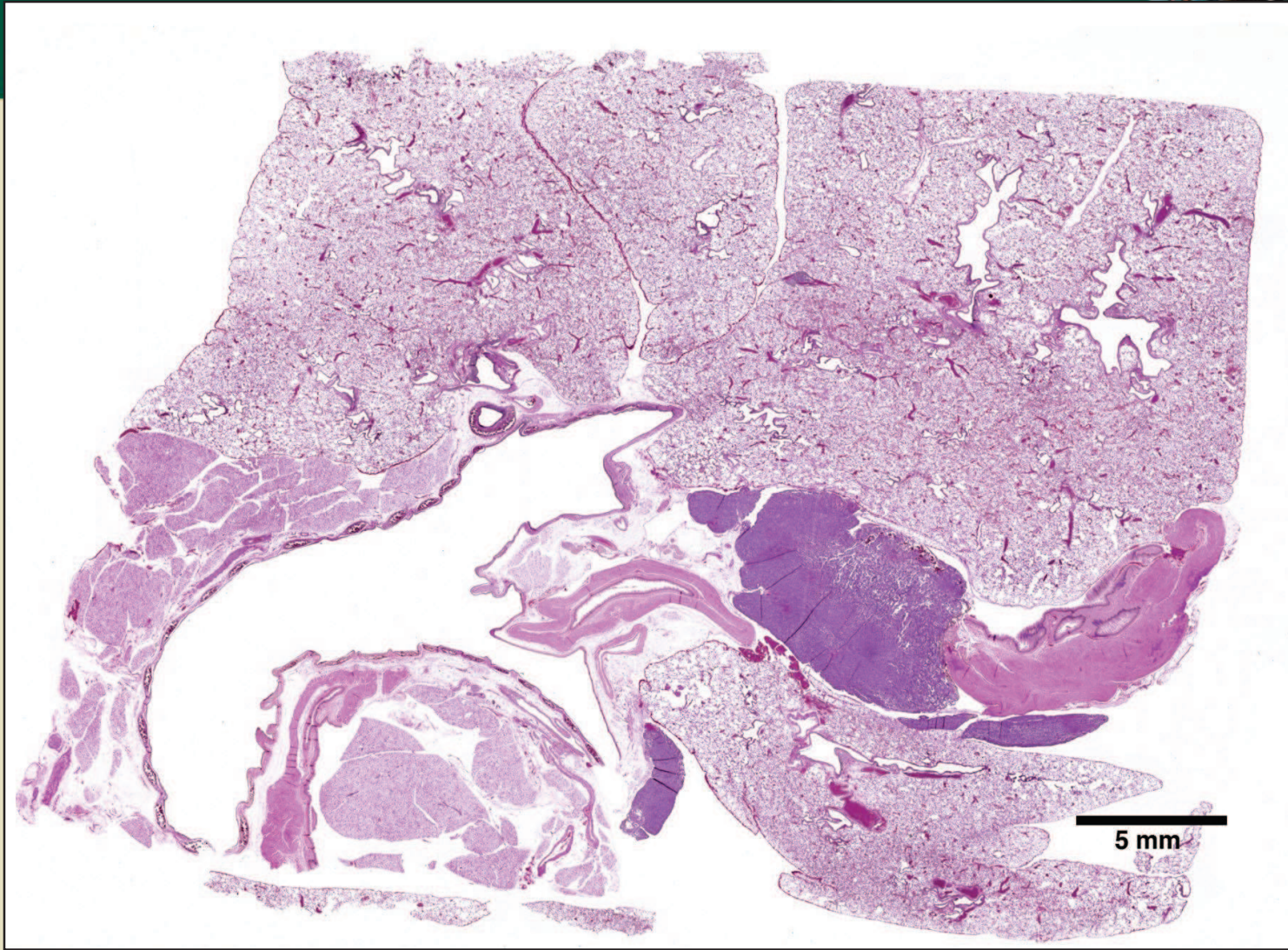
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Research Triangle Park, North Carolina, USA*

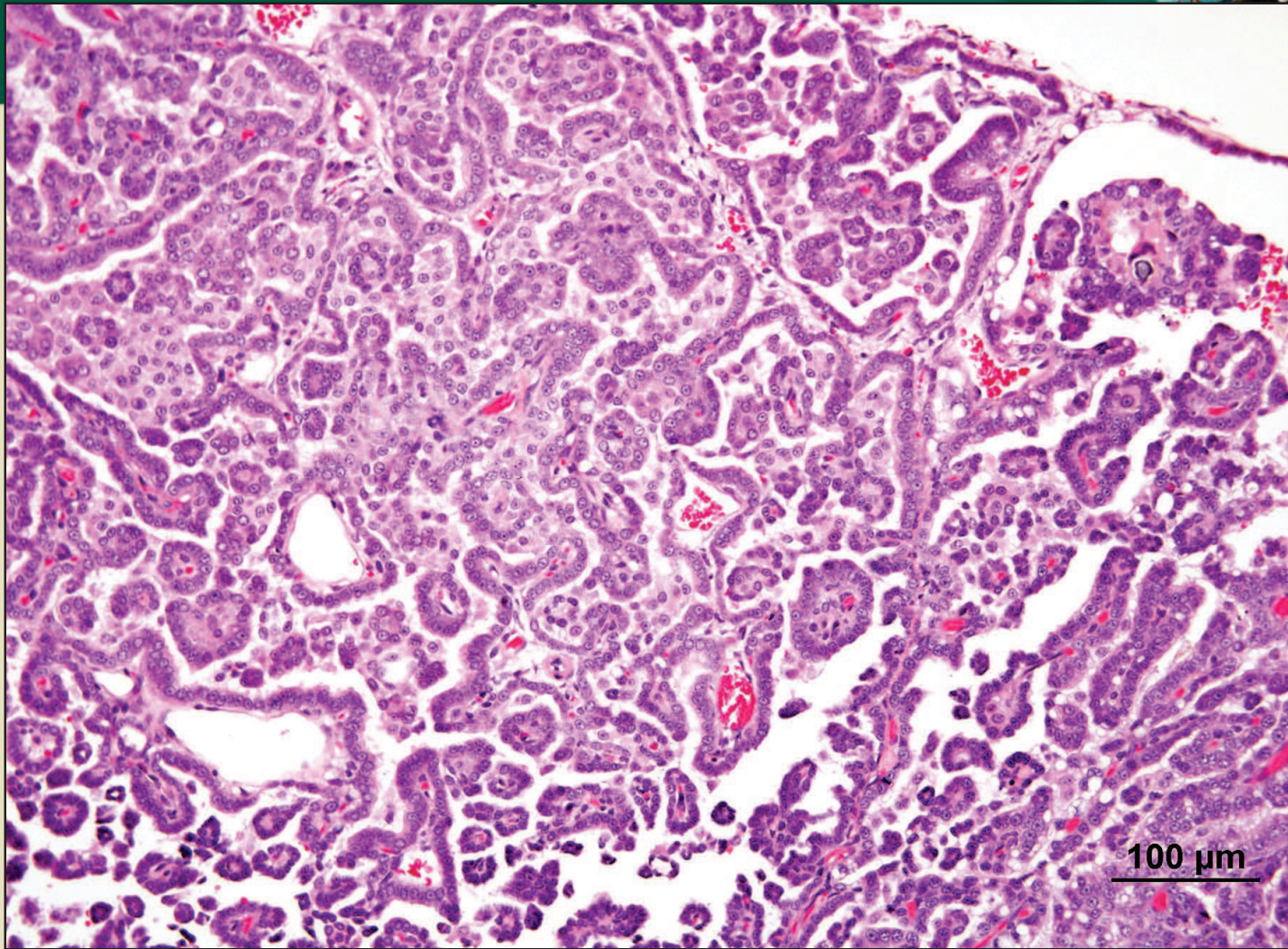
Howroyd et al., 2009






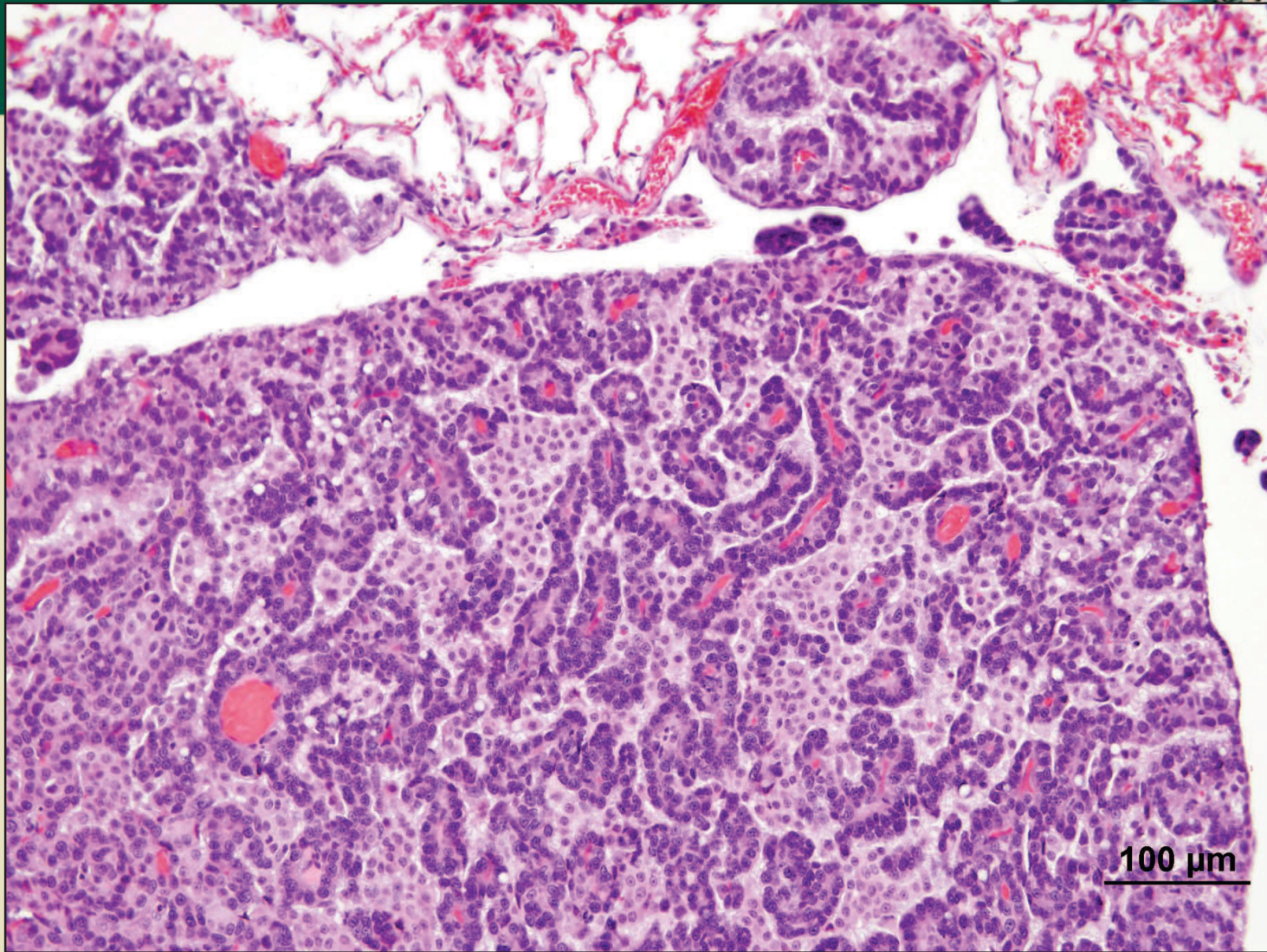
Mediastinal A/B Carcinomas

Howroyd et al., 2009

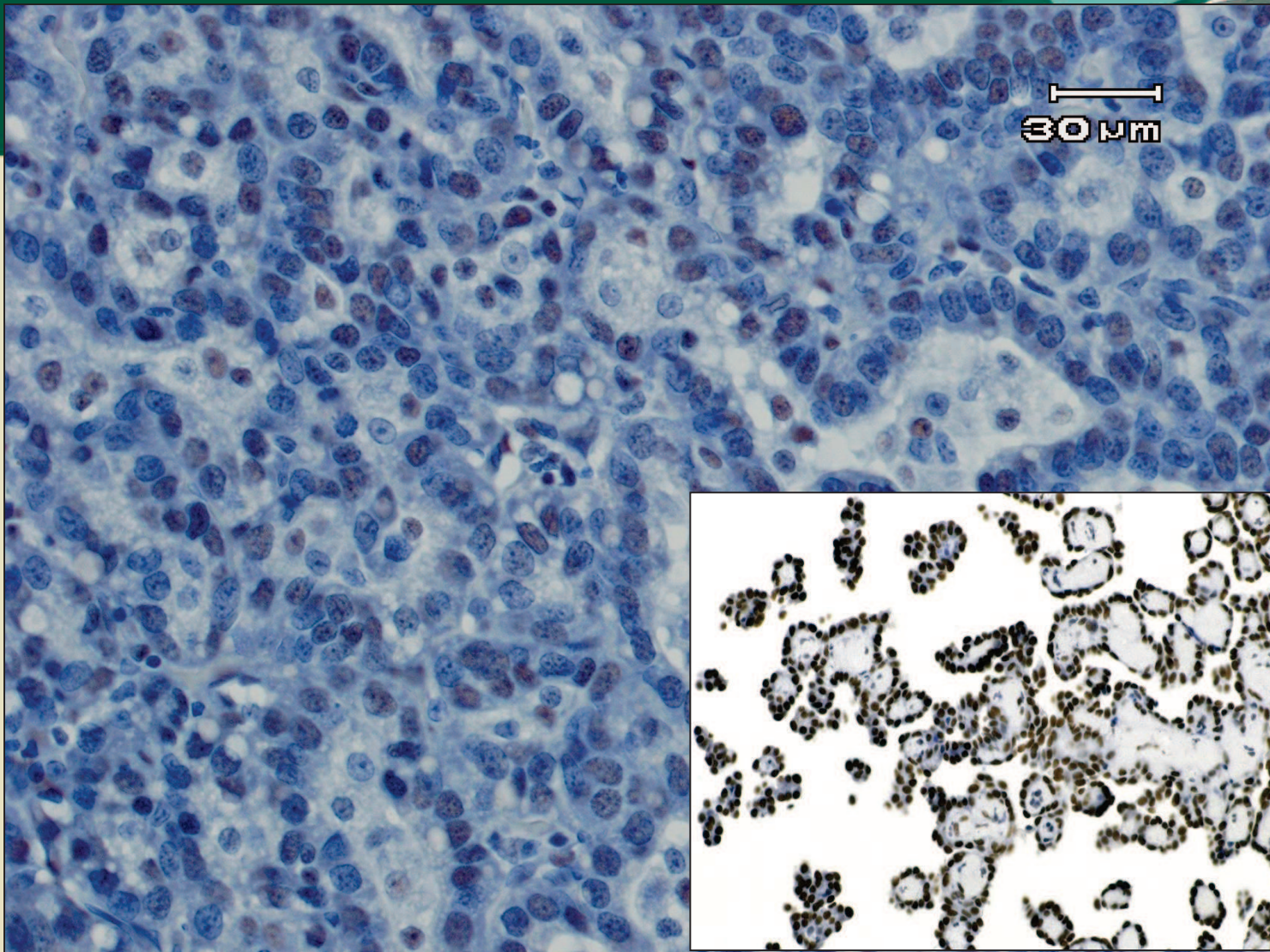


Mediastinal A/B Carcinomas

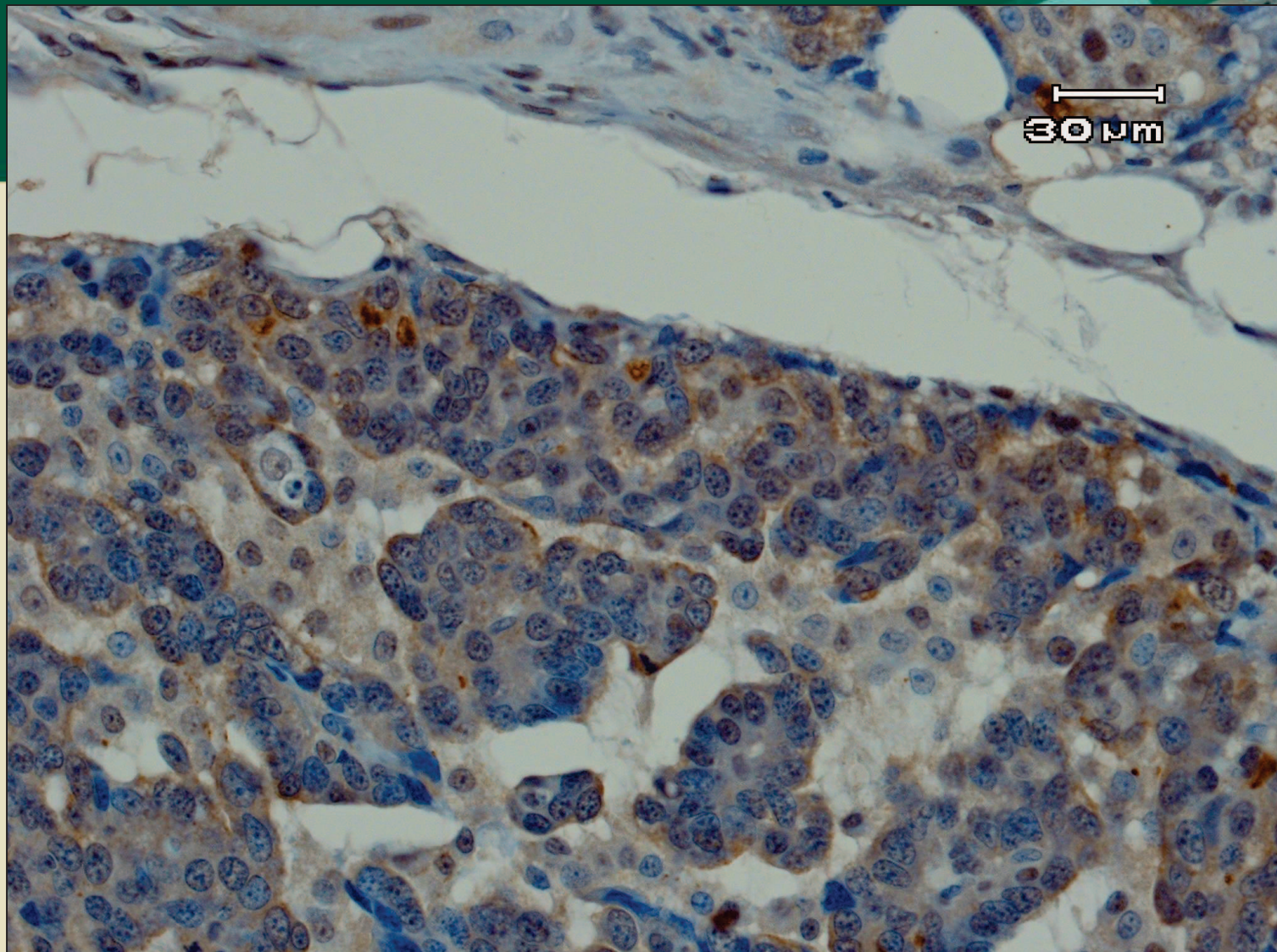
Howroyd et al., 2009 



Mediastinal A/B Carcinomas



Mediastinal A/B Carcinoma – Wilm's Tumor 1 (WT1) – Inset
Mesothelioma



Mediastinal A/B Carcinoma Surfactant Apoprotein A (SP-A) Staining



Other Applications of the Pathology Working Group

Histopathology of Nasal Olfactory Mucosa from Selected Inhalation Toxicity Studies Conducted with Volatile Chemicals*

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ABSTRACT

In recent years, histopathologic changes have been reported in the olfactory mucosa of rodents exposed, by inhalation, to a variety of volatile chemicals. In order to better characterize these lesions, a panel of experienced pathologists reviewed microscopic lesions of the olfactory epithelium of rats reported in 10 inhalation studies conducted with 8 different chemicals. The objectives were to determine if the olfactory epithelial lesions are morphologically similar or different for the chemicals of interest, to develop and recommend appropriate diagnostic criteria and nomenclature to characterize the morphology of these olfactory lesions, and to provide specific criteria for judging the degree of severity of the olfactory changes in these studies. The results indicated that the distribution and nature of the lesions were similar in all the examined studies in which olfactory changes were observed. Recommended standardized nomenclature and diagnostic criteria and a uniform method for scoring lesion severity based on the extent of distribution and severity of tissue damage are presented.

Keywords. Inhalation; olfactory epithelium; histopathology; grading severity

Benicar Carcinogenicity Concerns Resolved By Pathology Working Group

FDA was able to resolve concerns of carcinogenicity and genotoxicity related to Sankyo's antihypertensive *Benicar* (olmesartan medoxomil) through the formation of a "pathology working group" comprised of members chosen by both the sponsor and FDA, NDA review documents indicate.

Renal tumors seen in a two-year rat study initially concerned Office of Drug Evaluation I Director Robert Temple, MD, enough to recommend a "not approvable" action for the drug, which was ultimately approved April 25. Temple also was concerned by an increased incidence of hyperplasia in rat kidneys that

was difficult to distinguish from adenomas and by olmesartan's genotoxicity profile.

FDA's concern over toxicity was heightened by its general sense that Benicar is unremarkable in the angiotensin II receptor blocker (ARB) class. "The potential for carcinogenicity has been considered by the [Cardio-Renal Division] to be an approvability issue for an antihypertensive drug that has no unique clinical advantages over currently marketed members of its class," FDA said (*see preceding story*).

The decision to form a pathology working group came after reviews by the Carcinogenicity Assessment





Toxicol Pathol. 2007 Dec;35(7):928-41.

Histopathology of hemangiosarcomas in mice and hamsters and liposarcomas/fibrosarcomas in rats associated with PPAR agonists.

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Abstract

Peroxisome proliferator-activated receptors (PPAR) are involved in the pathogenesis of insulin resistance, diabetes, and related complications. Consequently, the identification of PPAR subtypes and the potential for their activation provides promising therapeutic targets for the management of type 2 diabetes mellitus. Available data from rodent carcinogenicity studies, however, demonstrate that PPAR agonists can be tumorigenic in one or more species of rodents at multiple sites. In 2005, the Health and Environmental Sciences Institute (HESI) PPAR Agonist Project Committee was established by a group of pharmaceutical companies to advance research on and to understand the modes of action and human relevance of this emerging rodent tumor data for PPAR agonists. Since the most commonly observed tumor types reported in rodents are hemangiosarcomas, fibrosarcomas and liposarcomas, the PPAR Agonist Project Committee approved a Pathology Working Group (PWG) to develop consensus of morphologic criteria for tumor diagnoses and consistency of diagnoses across multiple studies for hemangiosarcomas in mice and hamsters and liposarcomas/fibrosarcomas in rats. Therefore, the focus of the PWG review was to establish consistent tumor diagnostic criteria, to assess evidence of potentially preneoplastic changes and to identify distinguishing morphologic differences which may exist between spontaneous changes present in control animals with similar changes from treated animals. Specific diagnostic criteria and nomenclature are recommended for the classification of proliferative vascular lesions which may be present in mice or hamsters and for proliferative mesenchymal changes in rats in studies that are conducted with PPAR agonists.



Toxicol Pathol. 2008 Oct;36(6):769-76. Epub 2008 Sep 5.

Histopathology of the urinary bladders of cynomolgus monkeys treated with PPAR agonists.

Hardisty JF, Anderson DC, Brodie S, Cline JM, Hahn FF, Kolenda-Roberts H, Lele SM, Lowenstine LJ.

Experimental Pathology Laboratories, Inc., Research Triangle Park, North Carolina, USA.

Abstract

Peroxisome proliferator-activated receptors (PPAR) are involved in the pathogenesis of insulin resistance, diabetes, hyperlipidemias, and related complications. Consequently, a mechanistic understanding of PPAR subtypes and their activation provides promising therapeutic targets for the management of type 2 diabetes mellitus and the metabolic syndrome. Available data from rodent carcinogenicity studies, however, demonstrate that PPAR agonists can be tumorigenic in one or more species of rodents at multiple sites. Sufficient data are not yet available to explain the mode(s) of action for most of these tumor types. There has been information presented by FDA that indicates there are urothelial changes in the monkey (and possibly the dog) in addition to the rat. Outstanding questions exist regarding potency, species differences, safety margins, and other issues. In 2005, the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) PPAR Agonist Project Committee was established to advance research on the modes of action and potential human relevance of emerging rodent tumor data. Additionally, the HESI PPAR Agonist Project Committee authorized a Pathology Working Group (PWG) to examine the urinary bladder from cynomolgus monkeys. The focus of this PWG was to establish consistent diagnostic criteria for urothelial changes and to assess the potential relationship of these changes to treatment. Specific diagnostic criteria and nomenclature were recommended for the diagnosis of urothelial granules, vacuolation, hypertrophy, and hyperplasia in studies conducted with PPARgamma and dual alpha/gamma agonists in cynomolgus monkeys, which will assist investigators performing toxicity studies to provide data in a consistent manner between studies and laboratories. In this review of selected tissues, treatment with PPAR agonists was not associated with urothelial hypertrophy or hyperplasia, but there was an increased incidence in the size and frequency of vacuoles within the superficial urothelial and adjacent intermediate cell layers.



[Drug Chem Toxicol](#), 2010 Apr;33(2):131-7.

Pathology Working Group review and evaluation of proliferative lesions of mammary gland tissues in female rats fed ammonium perfluorooctanoate (APFO) in the diet for 2 years.

[Hardisty JE](#), [Willson GA](#), [Brown WR](#), [McConnell EE](#), [Frame SR](#), [Gaylor DW](#), [Kennedy GL](#), [Butenhoff JL](#),
Experimental Pathology Laboratories, Research Triangle Park, North Carolina, USA.

Abstract

Perfluorooctanoate (PFO) is a perfluorinated carboxylate that is widely distributed in the environment. A 2-year chronic study was conducted in rats fed either 30 or 300 ppm of ammonium perfluorooctanoate (APFO). To investigate the possible relationship of APFO exposure to proliferative mammary lesions, a Pathology Working Group (PWG) review of the original slides was performed. The consensus reached by the PWG was that the incidence of mammary-gland neoplasms was not affected by chronic dietary administration of APFO. Therefore, feeding female rats up to 300 ppm of APFO resulted in no increase in proliferative lesions of the mammary tissue.



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