Pathology Peer Review Process and Selected Lesions for the 2-Year Study of Cell Phone Radiofrequency Radiation in Rats

Mark F. Cesta, DVM, PhD, DACVP
Cellular and Molecular Pathology Branch
National Institute of Environmental Health Sciences

NTP Technical Report Peer-Review Meeting
March 26-28, 2018
• Pathology peer review process for the 2-year cell phone radiofrequency radiation (RFR) study in rats

• Heart, brain, and kidney lesions in the 2-year cell phone RFR study in rats
Standard NTP Pathology Peer Review Process

1. Pathology Data Review (PDR)

2. Audit of Pathology Specimens (APS)

3. Quality Assessment Review (QA)

4. Pathology Working Group (PWG)

5. +/- Pathology Peer Review (PPR)
Cell Phone Pathology Peer Review Process

- Potential treatment-related proliferative heart and brain lesions were initially selected for early reporting (i.e., partial report)
  - Complete review of these lesions (APS, PDR, QA, PWG) was conducted
    - 100% of materials reviewed in Audit of Pathology Specimens
  - Expedited review due to potential public health importance
    - Assigned multiple pathologists
    - Rapid turnaround
Cell Phone Pathology Peer Review Process

- Four Pathology Working Groups (PWGs) were convened
  - Initial PWGs were conducted as part of our normal process and underscored the need to develop definitive diagnostic criteria for these lesions
  - Two additional PWGs composed of specialists in neuro- and cardiovascular pathology conducted to develop these criteria
    - 5 external expert neuropathologists, including an MD pathologist with expertise in proliferative glial cell lesions in humans
    - 5 external expert cardiovascular pathologists
Cell Phone Pathology Peer Review Process

• After release of the partial report, the remaining tissues were reviewed according to our normal peer review process

• Several pathology peer reviews were conducted to address outstanding issues – some of these issues included data from the partial report
Cell Phone Pathology Peer Review Process

- All lesions that were potentially treatment-related were reviewed by panels of expert pathologists and the diagnoses and incidences represent a consensus of the pathology working groups.
Heart, brain, and kidney lesions

- **Heart**
  - Schwannoma
    - Endocardial
    - Myocardial (Intramural)
  - Schwann Cell Hyperplasia
    - Endocardial
    - Myocardial (Intramural)
  - Cardiomyopathy, Right Ventricle

- **Brain**
  - Malignant Glioma
  - Glial Cell Hyperplasia

- **Kidney - Chronic Progressive Nephropathy**
Heart, brain, and kidney lesions

Diagnostic Criteria – Endocardial Schwannoma

- Typically arises in subendocardial region of left ventricle
- Invasive (into the myocardium)
- Cells have indistinct cell boundaries
- Usually comprises two cell types
  - Ovoid cells (typically adjacent to endocardium)
  - Spindle-shaped cells
- Cells may exhibit mild atypia
- Mitotic figures may be present
- May see palisading nuclei
Heart, brain, and kidney lesions

Endocardial Schwannoma
Endocardial Schwannoma

Heart, brain, and kidney lesions
Endocardial Schwannoma
Endocardial Schwannoma

Heart, brain, and kidney lesions
Heart, brain, and kidney lesions

Diagnostic Criteria – Myocardial Schwannoma

- Often less cellular than endocardial schwannomas
- Lesion margins are indistinct
- Composed of loosely arranged spindle-shaped cells
- Mitotic figures and mild cellular atypia may be present
- May see palisading nuclei
Myocardial Schwannoma

Heart, brain, and kidney lesions
Heart, brain, and kidney lesions

Myocardial Schwannoma
Similar to Schwannoma, except:

- Less extensive than schwannoma
- Noninvasive (though proliferation along existing nerve tracts may give the appearance of invasion)
- There is no cellular atypia
- Mitotic figures are rare

May also occur in the myocardium
Endocardial Schwann Cell Hyperplasia

Heart, brain, and kidney lesions
Heart, brain, and kidney lesions

Endocardial Schwann Cell Hyperplasia

RV
Heart, brain, and kidney lesions

Endocardial Schwann Cell Hyperplasia
Diagnostic Criteria – Cardiomyopathy

- Degeneration, necrosis, or loss of cardiomyocytes
- +/- mild inflammation – macrophages and lymphocytes with occasional neutrophils
- Fibrosis in later stages of disease
- In right ventricle, most prominent in subepicardial region in lower half of heart (toward apex)
Cardiomyopathy

Heart, brain, and kidney lesions
Heart, brain, and kidney lesions

Right Ventricle – Cardiomyopathy
Heart, brain, and kidney lesions

Right Ventricle – Normal

Right Ventricle – Cardiomyopathy
NTP testing and research strategies

Brain Sampling

From 3 to 7 Sections of Brain

Original

New Sampling
Diagnostic Criteria – Malignant Glioma

- Neoplasms are usually larger than glial cell hyperplasia
- Indistinct lesion borders
- Cells are usually pleomorphic and densely packed
- Perivascular cuffing
- +/- Satellitosis
- +/- Meningeal invasion
- +/- Mitotic figures (few)
Malignant Glioma

Heart, brain, and kidney lesions
Heart, brain, and kidney lesions

Malignant Glioma
Heart, brain, and kidney lesions

Malignant Glioma
Malignant Glioma

Heart, brain, and kidney lesions
Malignant Glioma

Heart, brain, and kidney lesions
Diagnosis Criteria – Glial Cell Hyperplasia

• Similar to malignant glioma except:
  – Usually smaller
  – No meningeal invasion
  – Cell density is low
  – +/- Perivascular cuffing (minimal if present)
  – Generally, no mitotic figures

• Additionally, no reactive, degenerative, or necrotic elements with the associated parenchyma
Heart, brain, and kidney lesions

Glial Cell Hyperplasia
Glial Cell Hyperplasia

Heart, brain, and kidney lesions
Heart, brain, and kidney lesions

Glial Cell Hyperplasia
Glial Cell Hyperplasia

Heart, brain, and kidney lesions
Heart, brain, and kidney lesions

Normal Brain

Glial Cell Hyperplasia

Malignant Glioma
Kidney – Nephropathy, Chronic Progressive and Related Lesions

- Considered main reason for decreased survival in control group
- Numerous lesions with decreasing incidences and/or severity were considered to be secondary to chronic progressive nephropathy (see draft NTP Technical Report for rats, Table 29, pg. 113)
  - Parathyroid Gland – Hyperplasia
  - Bone – Fibrous Osteodystrophy
  - Mineral in numerous organs
  - Polyarteritis nodosa (vascular inflammation) and secondary necrosis, degeneration, ulcer, erosion, etc.
Heart, brain, and kidney lesions

Diagnostic Criteria – Chronic Progressive Nephropathy

- Tubular epithelial cell regeneration (increased basophilia, cell size, and cell number)
- Basement membrane thickening around tubules
- Mononuclear inflammatory cell infiltrates
- Tubular dilation
- Tubular epithelial cell hyperplasia
- Tubular epithelial cell atrophy
- Protein casts within tubules
- Glomerular changes
Heart, brain, and kidney lesions

Chronic Progressive Nephropathy

Control – Grade 4

3.0 W/KG CDMA – Grade 1
Chronic Progressive Nephropathy

Heart, brain, and kidney lesions

3.0 W/KG CDMA – Grade 1
Chronic Progressive Nephropathy

Heart, brain, and kidney lesions
Thank you