NTP
National Toxicology Program

NTP Study PFOA Chronic Toxicity and Carcinogenicity with and without Perinatal Exposure

Pathology Peer Review Process

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Phases of the Pathology Review

- **Step 1** - Study Pathologist Review
- **Step 2** - Pathology Peer Review
  - Multi-step process
  - Directed by an NTP pathologist

Society of Toxicologic Pathology Guideline

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Best Practices Guideline: Toxicologic Histopathology

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Step 1 - Study Pathologist Review

- Performed at the study laboratory.
- Supervises necropsies.
- Performs the initial, independent, microscopic evaluation of all tissues.
- Prepares report of pathology findings that is included in the final study laboratory report.
- Data is locked, i.e. no additional changes can be made.
- Pathology materials and data sent to the NTP Archives.

Step 2 - NTP Pathology Peer Review

Multi-step Process

- **Directed by an NTP Pathologist**
  - Pathology Data Review
  - Audit of Pathology Specimens
  - Pathology Quality Assessment Review
  - Pathology Working Group (PWG) Review
    - PWG Pathologist Review
    - PWG Panel Review
  - Pathology Data Audits

Objectives

- Re-evaluate all diagnoses in the suspected target organs/tissues.
- Evaluate the precision of the pathology data.
- Ensure that treatment-related effects are:
  - Properly identified
  - Consistently diagnosed
  - Correctly interpreted
- Identify pathology issues to address before the pathology data are reported.
- **Establish confidence in the pathology data**.

Pathology Data Review (PDR)

- **Independent** review by a second pathologist - Quality Assessment Pathologist (QAP).
- Detailed review of microscopic diagnoses listed in the summary incidence tables to:
  - Confirm suspected target organs and treatment-related effects
  - Identify terminology problems
    - Inconsistent use
    - Errors
    - Duplications
  - Concurrent control tumor incidences that vary from historical controls
- Also review:
  - In-life/clinical signs
  - Necropsy records
  - Macroscopic findings
  - Body weights tables
  - Organ weight tables
  - Clinical pathology records
- PDR Report
  - List subset of organs/lesions for review
  - **Guide for the Quality Assessment and Pathology Working Group reviews**

Audit of Pathology Specimens (APS)

- **Quality control step**.
- Specimens from a random 10% of animals examined.
  - All organs/tissues were properly sampled at necropsy
  - All potential lesions observed at necropsy were collected
  - Correctness of animal identifiers
  - Accounting of tissue blocks and histology slides
  - Tissue blocks and histologic slides
    - Accurately labeled
    - Properly prepared
- Results of the audit documented in the PDR report.

PDR Recommendations for PFOA QA Review

- **All tumors (all animals/groups)**
- **Organs reviewed for all diagnoses (target organs; all animals/groups)**

Male	*Female*
Liver	Liver
Pancreas, acinus	Pancreas
Pancreas, Islets	Pancreas, Islet
Kidney	Kidney
Testes	Uterus
	Stomach, forestomach
	Stomach, glandular
	Thyroid Gland

- **Organs reviewed for specific diagnoses (all animals/groups)**

Male	*Female*
Thyroid Gland – Hyperplasia	Lymph node, Mandibular – Atrophy
Prostate Gland – Inflammation	Lymph node, Mesenteric – Atrophy
Adrenal Medulla – Hyperplasia	Spleen – Atrophy
	Bone marrow – Atrophy
	Pituitary Gland – Hyperplasia
	Mammary Gland – Hyperplasia

- **Specific diagnoses for review (only when lesion diagnosed)**
  - Possible diagnostic duplications
  - Questionable terminology
  - Unusual incidences

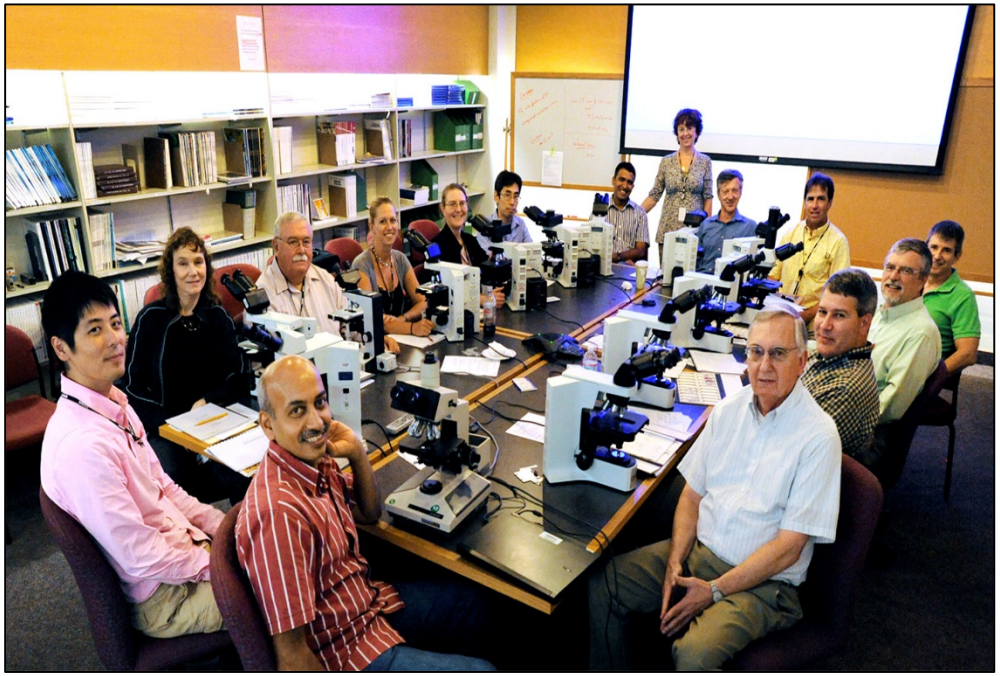
Pathology Quality Assessment Review

- Selective review of the Study Pathologist's findings by the Quality Assessment Pathologist (QAP).
- Review guided by the recommendations of the PDR.
- **Independent** review of the slides by the QAP.
- Confirm/identify suspected treatment-related effects.
- Verify the accuracy of the diagnoses.
- Ensure terminology consistent within the study and compared to previous NTP studies.
- **NTP pathologist resolves most diagnostic differences between the SP and the QAP.**
- **Unresolved differences resolved during the Pathology Working Group review.**

Pathology Working Group (PWG) Review

- Two-stage review:
  - PWG Pathologist/Coordinator Review
  - PWG Panel Review
- **Independent** review by a third pathologist (*Pathology Working Group Pathologist/Coordinator*).
- Reviews same slide set reviewed by the QAP.
- Confirm the treatment effects and diagnoses.
- Resolve remaining diagnostic differences between the SP and the QAP.
- Select examples of lesions for reviewed by the PWG panel of pathologists.

Pathology PWG Panel Review



PWG Coordinator

Study Pathologist

QA Pathologist

NTP Study Pathologist

Toxicologic Pathologists

PWG Panel Review

- Final confirmation of pathology findings.
- Review slides of representative lesions.
- By consensus vote:
  - Confirm suspected treatment-related effects
  - Resolve diagnostic and terminology differences between the SP, QAP and the NTP pathologists
  - Agree or disagree on:
    - New diagnoses recommended for addition
    - Diagnoses recommended for deletion

Finalization of Data

- Pathology data updated to reflect changes identified during QA and PWG reviews.
- Independent audit of all (100%) updated pathology data to verify changes made.
- Pathology data updated based on the audit results.
- Final pathology incidence and statistical are tables generated.
- Data posted to the NTP website.

Questions