

CONTRACT CONCEPT REVIEW

**NTP Board of Scientific Counselors Meeting
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Concept Title: Pathology Peer Review for NTP Studies and Support for the NTP and other Divisions of the NIEHS

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Purpose

We propose having contracts, with two major purposes, which are to provide:

- 1. Independent pathology peer review for NTP studies (80%).** The peer review includes, but is not limited to, evaluation of pathology records, evaluation of the pathology diagnoses and comparison with the histological material, and evaluation of clinical pathology specimens and clinical pathology data. It is anticipated that over 60 studies per year will be subjected to peer review.
- 2. Pathology support for NTP and other NIEHS projects (20%).** Pathology support includes providing staffing, necropsy, histology, special techniques, electron microscopy, molecular pathology, training, and histopathology evaluation for NTP and NIEHS investigations, as well as providing reports and continuing education relative to issues identified during peer review. It is anticipated that at least 50 projects will be performed yearly as support for NTP and NIEHS.

Background and Significance

The NTP evaluates the toxicity and carcinogenicity of agents of environmental concern by exposing rats and mice by appropriate routes (feed, water, inhalation, dermal, etc.) to various doses of the agents. These are conducted by a variety of testing laboratories under contract to the NTP. Since a program of the magnitude and diversification of the NTP requires cooperation and collaboration of numerous testing laboratories throughout the nation, there is a need for assessment of uniformity and accuracy of pathology data and diagnostic criteria and procedures. The recognition of a need for independent verification of the pathological findings resulted in the first pathology peer review contract being awarded by National Cancer Institute (NCI) in 1978 for their long-term carcinogenicity studies. The current NTP contracts have been in place since 1984. Implementation of the pathology peer review mechanism led to a marked improvement in the quality of pathology data from NTP studies including: (1) correction of erroneous or inconsistent data, (2) improved initial evaluations resulting from feedback provided to laboratory pathologists, (3) improved study design by NTP personnel, and (4) identification of special pathology issues that were subsequently addressed in pathology conferences. For more than 30 years, the NTP has been recognized both nationally and internationally for its rigorous pathology review process and for high quality pathology data from its studies.

NTP Pathology Peer-Review Process

The NTP pathology peer-review process is rigorous and an integral part of providing high quality pathology data for NTP Technical, Toxicity, and Genetically Modified Model Report series. NTP toxicity and carcinogenicity studies yield large amounts of data, including data from pathology evaluations of necropsied animals in all phases of the testing protocols.

- Chronic studies are usually 2-year exposures, with or without perinatal exposure, and in some cases have interim time points, typically at 9 and/or 15 months. Chronic studies generally comprise at least 800 animals (usually 3 dose groups plus one control group, 50 animals per group, both sexes, and include both rats and mice). Each study produces an average of 14 slides containing about 40 tissues per animal, for a total of approximately 12,000 slides and 30,000 tissues.
- Subchronic studies are usually 90-day exposures (5 dose groups plus controls, both sexes, in rats and mice). Each study produces an average of 11 slides per animal, or a total of approximately 2,600 slides.
- Genetically modified model (GMM) animal studies are typically of 26- or 39-week duration and performed in genetically altered mouse strains such as tp53def (p53+/-heterozygous), Tg.AC (v-Ha-ras transgene) or p16^{INK4a} heterozygous knockout mice. Each study includes 2 sexes, 15 animals per group, 3-5 doses groups, plus controls. Each study produces an average of 10 slides (range ~5-20) per animal and an average of about 1400 slides (range ~1000-2000).

The NTP also carries out developmental and reproductive toxicology studies (DART) including reproductive and continuous breeding (RACB) studies, as well as modified one-generation (MOG) studies, immunotoxicity studies, molecular pathology studies, and neurotoxicity studies. The DART/RACB studies have thousands of slides including vaginal cytology for estrus staging, stage awareness for spermatogenesis, and evaluation of mammary gland whole mounts. MOG studies may have up to 5 cohort studies.

The main purpose of the pathology peer-review process is to achieve consensus on pathology diagnoses of all neoplasms, unusual lesions, and treatment-related neoplastic and non-neoplastic lesions. This is accomplished by resolving diagnostic discrepancies that arise during the pathology review of NTP studies. The NTP pathologist assigned to that study oversees the entire process. Through contract support, the initial gross and microscopic pathology evaluation for each study is conducted by a pathologist at the study laboratory (called study pathologist). The pathology findings generated at the study laboratory are then subjected to a multi-level pathology review and an audit of pathology specimens (APS). The first level of review is called the pathology data review (PDR), which defines what exactly needs to be examined during the pathology quality assessment (PQA), which is conducted by a second contractor pathologist. The next review is by a third pathology contractor, called a pathology working group coordinator followed by review of selected findings at a pathology working group (PWG). The PWG review resolves any possible discrepancies, reviews possible treatment-related lesions, achieves consensus, and represents the culmination of the NTP pathology review process. The findings after the PWG are considered the “final pathology results.” These results form the basis for the analysis of the findings, development of study conclusions by NTP staff, and preparation of the draft report in the appropriate NTP report series.

Pathology Support for NTP and NIEHS

Pathology assessments, particularly histopathological evaluations of tissues, are critical and integral components of all studies. Important goals of the complete pathological evaluation of studies performed by the NTP and NIEHS are to: (1) improve the understanding of the nature of chemically induced lesions in rodents; (2) develop criteria and standardized terminology to facilitate consistent diagnosis, documentation, and interpretation of the lesions observed; and (3) ensure uniformity, consistency, and accuracy of the diagnostic criteria and pathology procedures used. Routinely, these goals are accomplished through a variety of pathology tasks, which are performed by qualified professionals (anatomic pathologists, molecular biologists, etc.) and technical staff (pathology assistants, histotechnologists, etc.), prior to, during, and after completion of a study as part of the APS, PDR, PQA, and PWG reviews of studies. Furthermore, as study results become available, the need often arises to

perform additional evaluations and studies to further define the toxicity and/or carcinogenicity of the chemical under study, and the mechanisms that may be involved. Such studies may include additional routine gross and/or histopathological evaluations, the measurement of cell replication and apoptosis, or the application of specialized procedures such as immunohistochemistry, electron microscopy, or morphometrics.

In addition, research conducted by in-house NIEHS/Division of Intramural and NIEHS/Division of NTP investigators frequently requires routine and/or specialized pathological support and evaluations before the studies can be completed and the results reported, usually in the peer-reviewed literature. These activities require a high level of professional and technical pathology support, maintaining the same high standards of uniformity, consistency, and accuracy of the diagnostic criteria and pathology procedures used for generation of the data. The use of the pathology contract support for these in-house studies helps maintain consistency in terminology and diagnostic criteria.

Proposed Changes to the Current Statement of Work

Under the proposed new contracts, the QA pathologist will also serve as the PWG coordinator and manage the PWG together with the NTP pathologist. Conduct of the PWG will be incorporated into the QA process, thereby streamlining the pathology review process overall and decreasing the time and cost to achieve final data.