

NTP hosts review of endocrine disruptor screening

By Eddy Ball

To help advance the U.S. Environmental Protection Agency (EPA) Endocrine Disruptor Screening Program (EDSP), NTP and NIEHS hosted a [Society of Toxicologic Pathology \(STP\)](http://www.toxpath.org/) (<http://www.toxpath.org/>) regional working meeting March 21 on pathology endpoints. The meeting attracted some 75 attendees, including NTP scientists [Darlene Dixon, D.V.M., Ph.D.](#), and [Paul Foster, Ph.D.](#), who participated in breakout sessions, following presentations by representatives of regulatory agencies, sponsors, and contract research organizations currently involved in these studies.

The attendees conducted a critical evaluation of EPA guidelines for conducting pathology assays of pubertal developmental and thyroid function in intact juvenile/prepubertal rats, which are part of the [890 series](http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series890.htm) (http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series890.htm) of endocrine disruptor assays, and developed recommendations that will be made available in 6 to 12 months as a best practices publication in the society's journal, *Toxicologic Pathology*.

The pubertal developmental and thyroid function assay guidelines are part of a comprehensive program, launched by congressional mandate in 1996, to evaluate the effects of endocrine disrupting compounds (EDCs) in humans and animals, using validated testing, much of it developed specifically for the program (see [text box](#)).

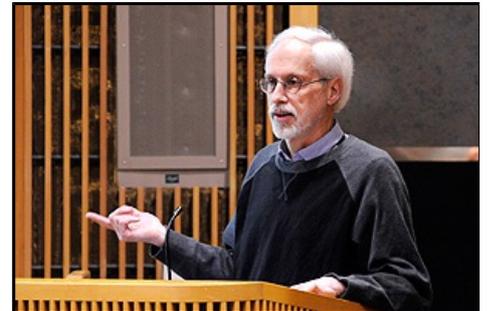
Part of the evolution to predictive toxicology

NTP Associate Director [John Bucher, Ph.D.](#), welcomed workshop attendees with an overview of NTP that helped place the animal testing, being considered in the workshop, within the context of the emerging paradigm of predictive toxicology under development by the Tox21 consortium. Bucher spoke to NTP's major focus on EDC exposure during development, and long-term health effects. Bucher pointed to five-generation estrogenic compound studies, and the bisphenol A clarity study underway in conjunction with the National Center for Toxicological Research (see [story](#)).

Although the main thrust of predictive toxicology is expanding *in vitro* high-throughput screening, Bucher and the speaker who followed him, EPA lead scientist [Doug Wolf, D.V.M., Ph.D.](#), (<http://toxforum.org/participant/doug-wolf-epa>) emphasized that streamlined rodent pathology studies, based on the principles of good laboratory practices, continue to be critical in decision-making. They agreed, as well, that regulatory agencies need to move forward using best practices achieved through the consensus of expert pathologists.



Dixon introduced Bucher, who was the first speaker at the meeting. Dixon was a member of the meeting organizing committee and co-leader of the Female Reproductive Assay Breakout Group. (Photo courtesy of Steve McCaw)



Bucher underscored NTP interests in developing new methods for studying EDCs, identifying new ways of integrating information about chemical toxicity, and advancing adequate and accurate pathology. (Photo courtesy of Steve McCaw)

The devil in the details

STP Education Committee consultant Kevin Keane D.V.M., Ph.D., served as facilitator for the meeting. As he emphasized, “This is an open meeting that is not on behalf of any one stakeholder in these assays, but rather is intended to be a collegial discussion of the science at hand.” On a humorous note, Keane described the meeting’s goal — “To reach a consensus, as much as you can get a group of pathologists to reach a consensus.”

Despite Keane’s tongue-in-cheek caveat, and the number of practical matters the group could not agree on, the group reached consensus on many important points, including the value of including the male mammary gland and female vagina as organs to study, as well as the use of humane practices for anesthetizing animals.

In remarks echoed by several of the speakers, Karen Regan, D.V.M., of Regan Path/Tox Services, noted there is also a pressing need for interpathology consistency, standardized methodology, and objectivity. “You don’t want to overanalyze these things,” she said. “Just describe what you see and interpret later.”

In their assessments of the Tier 1 screening, which examines very young animals after 20 to 30 days of exposure to a chemical beginning about three weeks after birth, several speakers pointed to the need for developmental touchstones. “You need to know the normal at this age of animals,” said Dianne Creasy, Ph.D., of Huntingdon Life Sciences. “The system needs to be considered as a whole, when you’re looking for endocrine disruption.”

Because streamlined rodent assays are uncharted territory for many pathologists, presenters and discussants agreed that a number of technical issues will need more discussion, consideration, and specific guidance. As a case in point, in her report on thyroid endpoints, Catherine Picut, V.M.D., J.D., of WIL Research, honed in on one major consideration, as she described the direction in the EPA guidelines to pick a representative area of tissue to describe.

“What does that mean?” she asked attendees. Tellingly, no one seemed to have a ready answer.



Keane urged attendees to pay attention to the very practical details involved in evaluating a long list of endpoints. Pointing to follicles in the ovary as an example, he asked, “Do you count this?” (Photo courtesy of Steve McCaw)



Wolf explained that the EDSP mandate arose from food quality protection and safe drinking water legislation, and concerns about estrogenic activity in humans. The program expanded later to include wildlife, androgen and thyroid hormone disruption, and agonistic and antagonistic effects. (Photo courtesy of Steve McCaw)



Although he wasn’t part of the working group, pathologist Gordon Flake, M.D., was one of several NTP scientists who were on hand for the morning talks, which drew a capacity audience to Rodbell auditorium. (Photo courtesy of Steve McCaw)



In her review of male screening, Creasy was critical of several of guidelines that called for examining just one testis and epididymis. “I don’t know why,” she said. “This is so bizarre.” The group agreed that, at the least, tissue selected for pathology should come from the same side of the animal. (Photo courtesy of Steve McCaw)



As an aside during his report on the Male Reproductive Assay Breakout Group, co-leader George Parker, D.V.M., Ph.D., of WIL Research, struck at the heart of the matter. “Our collective procedures are somewhat haphazard,” he said. “There really is some room for science here.” (Photo courtesy of Steve McCaw)



Foster, center right, echoed calls for a better understanding of young animals. “You have a much bigger range of normal,” he said. “They are immature. The system isn’t running yet.” (Photo courtesy of Steve McCaw)



At the close of their long day of deliberation, most of the participants gathered on the patio outside the Rall building. (Photo courtesy of Steve McCaw)

After a slow start, EDSP gains momentum

Following careful reviews by experts, in 2009, EPA announced the initial list of chemicals to be screened for their potential effects on the endocrine system, or Tier I testing, and issued requests for data. Testing will eventually be expanded to cover all pesticide chemicals, as well as substances that may occur in sources of drinking water to which a substantial population may be exposed. EDSP involves a battery of *in vivo* and *in vitro* assays of endocrine endpoints in amphibians, fish, rats, and humans.

Through Tier 1 screening, the program hopes to identify chemicals that have the potential to interact with the endocrine system. Tier 2 testing will determine the endocrine-related effects caused by each chemical, and obtain information about effects at various doses.

Endocrine disruptor screening is currently proceeding on three fronts — developing and validating Tier 2 tests; selecting chemicals for screening and testing; and implementing the policies and procedures the agency will use to require screening.

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