NTP
National Toxicology Program

Hormonally-Induced Reproductive Tumors: Relevance of Rodent Bioassays

May 22-24, 2006 in Raleigh, NC

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National Institute of Environmental Health Sciences

Background

- **3rd workshop in a series to implement the NTP Vision and Roadmap for the 21st century**

- **Why this topic?**
  - The NTP is confident in our ability to detect genotoxic carcinogens, less confident about our ability to detect carcinogens with some other modes of action (e.g., hormonally-mediated) and their prediction of the same end point in humans.
  - Some modes of hormonal action for induction of tumors are not considered relevant for humans by regulatory agencies
  - Tumor sites selected based on suspected weakness in current NTP models and tumor prevalence

Format

- **Structure**
  - 1st day: Background talks (clinical/ epidemiology, rodent models, modes of action)
  - 2nd day: Breakout group meetings
  - 3rd day: Breakout group reports
- **Participants**
  - ~ 55 invited attendees (clinicians, laboratory investigators, epidemiologists, pathologists, statisticians, risk assessors)
  - ~ 60 members of the public from government, academia, industry, and non-profit organizations
  - many generators and users of bioassay and NTP data

Charge

Determine the adequacy and relevance to human disease outcome of rodent models for four types of hormonally induced reproductive tumors

- ovary
- mammary gland
- prostate
- testis

Summary Responses to Charge

- **Ovary**
  - Existing rodent models are not useful
  - Certain transgenic and *in vitro* models may be more predictive, but need to be evaluated
- **Mammary Gland**
  - Not enough data to evaluate false negatives/positives
  - Rat is a better model than the mouse
- **Prostate**
  - Current NTP models (and most other non-transgenic models) are not useful (don't see chemically-induced tumors)
  - NTP should consider using a more sensitive model, especially when the prostate is a suspected target from MOA, or other information.
- **Testis**
  - Can be sensitive for detecting Leydig cell tumors, but not germ cell tumors

Cross-Cutting Issues for NTP

- Re-consider use of the F334 rat
  - insensitive model for certain types of tumors (i.e., testicular tumors, mammary gland fibroadenomas)
  - high background of leukemia can complicate overall pathology interpretation
- Add interim necropsies to help distinguish chemically-induced tumors from background incidence (especially important for high background tumor sites)
- Make tissues available for research purposes that could be used to inform on modes of action
- Include additional endocrine responsive endpoints (e.g., periodic vaginal smears, whole mount of mammary gland)
- Keep some study components standard for comparability, but be able to customize
  - Better utilize information from subchronic or other preliminary studies (*In utero* 90-day, short-term *in vitro,* and *in vivo* screens) that might trigger changes

Cross-Cutting Issues for NTP

- Consider use of different models to detect effects when appropriate (e.g. post-pregnancy exposure, alternative model when prostate is a suspected target site)
- Evaluate the importance of developmental programming in hormonally dependent tissues leading to pre-neoplastic events and tumors
  - Consider using an F_1 cohort from NTP reproduction studies (in the SD rat) in chronic bioassays
- Differentiate between hormonally-induced versus hormonally-mediated pre-neoplastic events and tumors
- How would we know if we had a predictive model?
- For some important human tumors the standard models are insensitive
  - tumor prevalence differences (i.e., ovarian epithelial cell tumors, mammary gland metastasis, testicular germ cell tumors)
  - anatomical and histological differences (i.e., prostate, ovarian stromal tumors)

Future Activities

- Workshop Report
  - A brief synopsis of the workshop and NTP perspective
  - Published in the peer-reviewed literature
- NTP Actions
  - NTP staff will synthesize input from all the NTP Roadmap & Vision workshops this fall
    - 4th workshop: “Biomarkers for Toxicology Studies” (September 21-22, 2006 at NIEHS)
  - Proposed NTP actions presented at a future BSC meeting

Meeting Materials

Agenda, presentations, background materials, participant lists, etc. can be found on the NTP website:

http://ntp.niehs.nih.gov/

see "Meetings & Workshops"

direct URL:

http://ntp.niehs.nih.gov/go/18592

Acknowledgements

- **Chairs and Rapporteurs**

Vernon Walker (Plenary Chair)

Breakout Group	Chair	Rapporteur
Mammary Gland	Dale Sandler	Nigel Walker
Ovary	Paul Terranova	Michael Wyde
Prostate	Bob Maronpot	Scott Masten
Testis	Bob Chapin	David Malarkey

- Speakers, Breakout Group Panels, Public Attendees
- Organizing Committee

"All models are wrong,

some models are useful"

George E.P. Box

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Invited Panel

Ovary

Paul Terranova, U of Kansas Medical Center (Chair)
Michael Wyde, *NIEHS/NIH* (Rapporteur)
Molly Brewer, *U of Arizona*
Charles Capen, *Ohio State U*
John Couse, *NIEHS/NIH*
Vicki Dellarco, *USEPA*
Warren Foster, *McMaster U*
Patricia Hoyer, *U of Arizona*
Grace Kissling, *NIEHS/NIH*
Peter Leung, *U of British Columbia*
Retha Newbold, *NIEHS/NIH*
Barbara Vanderhyden, *U of Ottawa*

Mammary Gland

Dale Sandler, NIEHS/NIH (Chair)
Nigel Walker, *NIEHS/NIH* (Rapporteur)
Robert Clarke, *Georgetown U*
Ralph Cooper, *USEPA*
Barry Delclos, *NCTR/FDA*
Richard DiAugustine, *NIEHS/NIH*
Sue Fenton, *USEPA*
Michael Gould, *U of Wisconsin*
Ruth Keri, *Case Western Reserve U*
Elizabeth Padilla Banks, *NIEHS/NIH*
Irma Russo, *Fox Chase Cancer Center*
James Stevens, *Wake Forest U*

Prostate

Robert Maronpot, NIEHS/NIH (Chair)
Scott Masten, *NIEHS/NIH* (Rapporteur)
Hans-Olov Adami, *Karolinska Institutet*
Gordon Flake, *NIEHS/NIH*
Simon Hayward, *Vanderbilt U*
John Isaacs, *John Hopkins U*
Abraham Nyska, *ILS*
Gail Prins, *U of Illinois – Chicago*
William Schrader, *NIEHS/NIH*
Tammy Stoker, *USEPA*
Mark Suckow, *U of Notre Dame*
Andrew Suttie, *ILS*
Douglas Wolf, *USEPA*

Testis

Robert Chapin, Pfizer (Chair)
David Malarkey, *NIEHS/NIH* (Rapporteur)
Jon Cook, *Pfizer*
Dianne Creasy, *Huntington Life Sciences*
Mitch Eddy, *NIEHS/NIH*
Paul Foster, *NIEHS/NIH*
Earl Gray, Jr.,*USEPA*
Jerry Hardisty, *EPL*
Marvin Meistrich, *U of Texas M.D. Anderson Cancer*
Shyamal Peddada, *NIEHS/NIH*
Jennifer Seed, *USEPA*
Niels Skakkebaek, *U of Copenhagen*

Breakout Group Questions (1)

- **Is there sufficient evidence to conclude that these tumors of the reproductive system in humans and experimental animals can result from an altered endocrine (i.e., steroid and pituitary hormones) milieu?**
  - Are tumor characteristics and the diagnostic criteria for tumor identification the same between rodents and humans? If not, what are the differences?
- **How useful are rodent models for predicting hormonally-induced reproductive tumors in humans?**
  - What pathological and physiological changes observed in rodent bioassays are assumed relevant for human predictions?
  - Are there any pre-neoplastic (e.g., hyperplasia) events observed in rodents that are considered predictive of human response?
- **What do we know of the proposed modes of action for the induction of these tumors in rodents or humans?**
  - Are there key events in the mode of action for hormonal tumors in general, or are they specific for each tumor type? If so, what are the common key events/ modes of action?

Breakout Group Question (2)

- **Exposure in the standard NTP rodent cancer bioassays typically commences with young adult animals. Are there any specific modes of action, or tumor types, for which an *in utero* exposure component should be the default experimental paradigm?**
  - How would we best design such studies? (time permitting)
- **The default approach for most cancer risk assessments is to assume linearity at low dose-response. Is this appropriate for these modes of action and tumor types?**
  - If not, what evidence would be required to move away from the default approach?
  - How do we (or should we) incorporate the concept of “additivity to background” when endogenous hormones are present with homeostatic control mechanisms?