UPDATE
National Toxicology Program
U.S. Department of Health and Human Services

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National Institute of Environmental
Health Sciences • NIH-HHS

What's Inside:

NTP board gives go ahead for PAH research and systematic review

By Robin Mackar reprinted from *eFACTOR*, January 2013

Evaluating NTP's approach to reaching conclusions for literature-based evidence assessments

Lynn Goldman, M.D., of George Washington University, served as the NTP BSC working group chair, and summarized the draft report to the board.

Left to right, Birnbaum, Bucher, Eastmond, and Mary Wolfe, Ph.D., director of the NTP Office of Liaison Policy and Review, listened carefully to public comments and board discussions on high profile topics. (Photo courtesy of Steve McCaw)

The report on evaluating NTP's approach for reaching conclusions for literature-based evidence assessments was developed by ten scientists representing academia, industry, and government. The draft provides comments and recommendations on each of the seven steps proposed for conducting the literature-based assessments.

"Overall, we felt the NTP's proposed approach for reaching conclusions for literature-based assessments was very proactive in increasing transparency," Goldman said.

In response to Goldman's comment, NIEHS/NTP Director Linda Birnbaum, Ph.D., underscored NTP's interest in getting public input. "There will be at least six opportunities for the public to comment, as we are conducting a systematic review," she said. "We want to be transparent and we want to have stakeholders involved."

When the NTP Board of Scientific Counselors (BSC) met on December 11, 2012, two main agenda items took center stage - polycyclic aromatic hydrocarbons (PAHs) and systematic review. The board endorsed NTP's multi-year PAH research concept with some minor tweaks, and accepted a working group report on systematic review.

Polycyclic aromatic hydrocarbons

Masten, who oversees the nomination and selection process for NTP studies, shared information about how the PAH research concept came to fruition. (Photo courtesy of Steve McCaw)

Scott Masten, Ph.D., who heads the NTP Office of Nominations and Selection, provided a brief introduction to the research concept on PAHs. Masten explained that an NTP concept represents a high-level look at the scope, approach, strategy, and direction that NTP would take in an area of interest, but is not to be thought of as a study design.

NTP toxicologist Cynthia Rider, Ph.D., lead for the PAH research effort, provided details about PAHs and the NTP approach to studying them. She said that PAHs are a large class of compounds found virtually everywhere in our environment. They occur naturally in petroleum and coal, or are created and released into the environment through natural events, such as forest fires and volcanoes. Rider noted that the 2010 Deepwater Horizon oil spill also reignited public concern over the human and ecological health hazards of PAHs.

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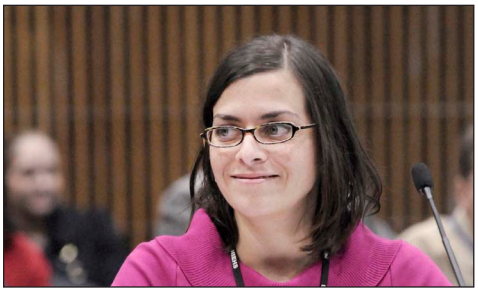
A flexible iterative process



Rider, who is relatively new to NTP, shared her extensive knowledge about PAHs with the board. (Photo courtesy of Steve McCaw)

"PAHs always occur in complex mixtures. There are at least 1,500 different PAHs, and there are numerous ways that humans can exposed, including through food, inhalation, or through the skin," Rider explained. NTP plans look at a variety of health effects, using a battery of toxicity tests, including experimental animals and cell culture systems.

Rider discussed the pros and cons of two different approaches for assessing cumulative effects of PAHs – the component-based, or relative potency factor approach, and the whole mixture approach. She said the NTP proposal would contribute data to both approaches, and that they would be flexible and iterative. "The testing program will be built in units, with each round of testing informing the next," Rider explained.

Using PAHs to move mixtures research forward

NTP plans to test both individual PAHs and complex environmental mixtures. Understanding how combined environmental exposures affect disease pathogenesis, or development, is a high priority for NIEHS and NTP. It is identified as Goal 4 in the NIEHS strategic plan and was the subject of a workshop in 2011.

Board members provided suggestions for moving the research forward, to ensure NTP looks at the breadth of endpoints or health effects PAHs may be causing, including endpoints relevant to known human effects.

"The board is supportive of the NTP's efforts to help us better understand the health effects from PAHs. This effort will also help move the whole field of mixture science forward," said BSC chair David Eastmond, Ph.D., of the University of California, Berkeley.

Board member Robert Chapin, Ph.D., of Pfizer, whole-heartedly agreed. "The NTP needs to be doing this. It needs to take on mixture science and wrestle it to the ground," he said.

Systematic review process

Most of the afternoon was spent discussing the NTP approach for systematic review that is being led by the NTP Office of Health Assessment and Translation (OHAT). Systematic review allows for more transparency of how NTP health assessment conclusions are determined (see story).

The board members listened to three public comments by phone and received all written public comments.

Both NTP Associate Director John Bucher, Ph.D., and Eastmond reminded the board that its charge was to accept or reject the NTP BSC draft working group report on the approach to systematic review. The board unanimously accepted the report (see text box).

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Upcoming Events

March 21-22, 2013

Peer Review of Draft Report on Carcinogens Monographs on 1-Bromopropane and Cumene

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

June 25-26, 2013

NTP Board of Scientific Counselors

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

September 24-25, 2013

Scientific Advisory Committee on Alternative Toxicological Methods

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

December 18-19, 2013

NTP Board of Scientific Counselors

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

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

Andrew Rooney, Ph.D., and Kris Thayer, Ph.D., of OHAT took turns walking the board through the draft approach, answering questions, and talking about next steps, including developing several case studies to show how the process works.

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison.)

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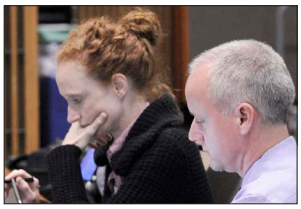

OHAT Director Thayer, left, and OHAT Deputy Director Rooney, reviewed their slides on the systematic review process, before presenting to board members. (Photo courtesy of Steve McCaw)

Evaluating NTP's approach to reaching conclusions for literature-based evidence assessments

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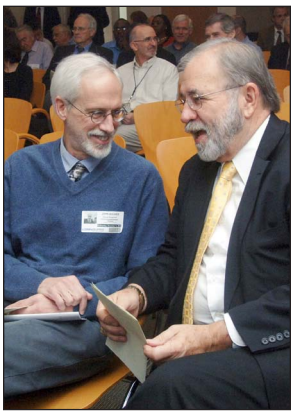
"Overall, we felt the NTP's proposed approach for reaching conclusions for literature-based assessments was very proactive in increasing transparency," Goldman said.

In response to Goldman's comment, NIEHS/NTP Director Linda Birnbaum, Ph.D., underscored NTP's interest in getting public input. "There will be at least six opportunities for the public to comment, as we are conducting a systematic review," she said. "We want to be transparent and we want to have stakeholders involved."

NIEHS/NTP celebrates 20-year partnership with FDA

By Cindy Loose reprinted from *eFACTOR*, December 2012



Bucher and Allaben enjoy a light moment during one of the breaks. (Photo courtesy of Cathy Brown)

A unique partnership between NIEHS and the U.S. Food and Drug Administration (FDA) has been so successful at protecting public health that countries around the world are seeking advice on how to implement a similar program, said NIEHS/NTP Director Linda Birnbaum, Ph.D., at a recent gathering celebrating the 20th anniversary of the collaboration.

Birnbaum was referring to the formal interagency agreement that was signed by both agencies in December 1992. The agreement makes it possible for NIEHS to provide support for toxicological studies on agents of public health concern that are conducted at the FDA (NCTR). Dozens of critical, complex studies carried out through this agreement have helped protect public health.

The National Toxicology Program (NTP) is an interagency program, headquartered at NIEHS, that coordinates and manages the efforts of the U.S. Department of Health and Human Services to understand the hazardous nature of chemicals to which the U.S. public is exposed. The interagency agreement between NIEHS and FDA is a critical mechanism by which these federal partners cooperatively work together to achieve these goals.

Milestones accomplished

At the anniversary ceremony November 14, at FDA headquarters in Silver Spring, MD, NTP Associate Director John Bucher, Ph.D., provided some key examples of how the collaboration between the agencies has impacted public health. He mentioned one study, in particular, that has helped improve the safety and quality of seafood imported from overseas.

"The work we've done together has really made a difference," said Jesse Goodman, M.D., FDA's chief scientist. He noted that one of the earliest studies looked at fumonisin B1, a toxin produced by fungi that grow on many types of corn and other grains. Considered the definitive study on the carcinogenicity of the fungi, the data were used around the world to set allowable contaminant levels in grains used in both animal and human food products.

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Coordinating through a committee of diverse partners can pose some challenges but, as Birnbaum noted, "The interagency agreement allows us to work together to develop common approaches to solve real public health questions."

Immediate practical applications

Weis, center, accepts her plaque for many years of dedicated service to the FDA and NTP from Goodman, left, and Birnbaum. (Photo courtesy of Cathy Brown)

NIEHS and FDA leadership prepare to dig into a tasty-looking cake prepared for the celebration. From left to right are Walker, Allaben, Birnbaum, Goodman, Bucher, and Paul Howard, Ph.D., director of the Office of Scientific Coordination at NCTR and FDA project officer on the NCTR/NIEHS interagency agreement. (Photo courtesy of Cathy Brown)

NTP Deputy Division Director for Science Nigel Walker, Ph.D., said studies take on a special dimension when you work with the people who need the data to make important regulatory decisions that can help protect lives.

"The public wants us to do the right thing, and this agreement allows us to work and spend wisely for public health," Walker said.

"Enormous efforts on the part of many people were needed to make the interagency agreement a success," said William Allaben, Ph.D., an early leader of NCTR. He singled out Connie Weis, who has worked at NCTR since 1997, and has been a program manager there since 2003. Weis, who is retiring from the FDA, was honored at the ceremony with a plaque. "I don't know what I would have done without her in my corner," said Allaben, who also thanked Birnbaum for "embracing us."

NTP toxicological studies carried out at NCTR have led to regulations of a number of ingredients in dietary supplements, animal feed, cosmetics, and in both human and veterinary pharmaceuticals. Potential health effects from exposure to bisphenol A, or BPA, is among the many studies currently ongoing.

The collaboration has advanced science and taken advantage of new scientific tools in state-of-the-art labs, to take on new challenges posed by emerging sciences. For example, in 2010, the FDA/NCTR and NIEHS/NTP, among others, collaborated to develop a Nanotechnology Core Facility to study potential health effects from rapidly developing nano-related products.

As Birnbaum concluded in her remarks, "The interagency agreement has produced 20 years of productive collaboration in science and research, and let's hope for many more."

(Cindy Loose is a contract writer with the NIEHS office in Bethesda, MD.)

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NTP panel reviews outcomes of women treated for cancer while pregnant

By Robin Mackar reprinted from *eFACTOR*, November 2012

The peer review meeting ran smoothly under the capable leadership of Spong, right. Birnbaum, left, and Bucher, center, listened closely to the discussions. (Photo courtesy of Steve McCaw)

A stellar peer review panel convened by the National Toxicology Program (NTP) provided input and invaluable medical, pediatric, pharmaceutical, and other expertise on the draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use During Pregnancy.

"We know very little about pregnancy outcomes of women being treated for cancer. This is an extremely important topic that hasn't been systematically looked at before," said NIEHS/NTP Director Linda Birnbaum, Ph.D., as she welcomed the nine-member panel of external experts to the October 1-2 meeting at NIEHS.

Under efficient chairmanship of Catherine Spong, M.D., associate director for Extramural Research at the Eunice Kennedy Shriver National Institute of Child

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Health and Human Development, part of the National Institutes of Health, and a board-certified obstetrician and gynecologist, the panel was able to have in-depth discussions and concur by unanimous vote on each of the NTP's five main findings.

Main findings

Howdeshell showcased what she had learned over the past two years, as she analyzed more than 430 published studies, on 52 cancer drugs, that reported pregnancy outcomes of female cancer patients treated with the drugs during pregnancy. (Photo courtesy of Steve McCaw)

One of the first findings, presented by the lead scientist for the evaluation, Kembra Howdeshell, Ph.D., of the NTP Office of Health Assessment and Translation (OHAT), focused on congenital malformations.

Both NTP and the reviewers agreed that the evidence showed that chemotherapy for treatment of cancer in the first trimester represents a higher apparent risk of major malformations than treatment in the second or third trimesters only. This finding confirmed current medical opinion and predictions, based on the timing of fetal organ development during pregnancy. However, the lead reviewers for each of the findings presented by Howdeshell acknowledged the imprecision in the data available to NTP, and called on the NTP to point out the limitations.

"I sympathize with those of you working on this topic. As someone who works in this area, I realize we all report things differently and our terminology is always changing. You can't make the data better – you can simply point out limitations," said Michael Greene, M.D., chief of obstetrics at Massachusetts General Hospital.

The panel also heard, and then voted on, additional health outcome findings, including the effects of chemotherapy on the risk of spontaneous abortion and stillbirth; pregnancy complications, such as reductions in amniotic fluid and fetal growth restriction; newborn weight and health; and growth development of the children. They again drew attention to data limitations and noted that some adverse effects, such as effects on the reproductive system and other organs, may not be apparent until later in life.

Research and outreach needs

The need for long-term follow-up studies of the gestationally exposed offspring was emphasized, as was the need for more easily accessible national registries for physicians to document cases. "There are so many research needs crying out for attention in this area," Greene emphasized. "For one, we need to get our colleagues to do a better job of developing quality case reports."

Other panelists, such as John Mulvihill, M.D., from the University of Oklahoma pediatrics department, a respected researcher on the topic of pregnancy outcomes following treatment with chemotherapy during pregnancy, suggested getting woman advocates, who have been successfully treated for cancer during pregnancy, to tell their stories. Panel member Janine Polifka, Ph.D., a developmental biologist in the department of pediatrics at the University of Washington, emphasized creating more awareness around resources already available for decision-making, such as OTIS, the Organization of Teratology Information Specialists, a nonprofit organization that provides information to patients and health care professionals about exposures during pregnancy and lactation.

Mulvihill called on the NTP to make clear, bottom line messages in its conclusions. After one of Howdeshell's presentations, he commented, "You are now the international expert on this topic. You will benefit the world with bottom line messages that can be understood by all. Be clear and spread your message widely."

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Howdeshell, who has been working with her OHAT colleagues, including Vickie Walker and Mike Shelby, Ph.D. (who recently retired), for nearly two years on this topic, gave a heartfelt thanks to all the panel members for their invaluable input. "This has been an incredible panel whose expert advice will surely make this document a state-of-the-science resource for both patients and physicians."

In offering his thanks and appreciation to the chair, his staff, and the reviewers, NTP Associate Director John Bucher, Ph.D., joked that it was the first time that all the research needs identified by a panel did not fall on the NTP alone. The final NTP monograph should be available by summer 2013.

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison.)

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Stokes selected as a fellow of ATS

Excerpted from *eFACTOR*, December 2012 article by Eddy Ball

Stokes joins a select group of scientists who are ATS fellows. Because of his leadership in the review and advancement of alternative testing for regulatory agencies, Stokes said he felt the recognition is especially gratifying.

National Toxicology Program (NTP) center director Rear Adm. William Stokes, D.V.M., was notified October 25 of his induction as a fellow of the Academy of Toxicological Sciences (ATS).

In his letter announcing the fellowship, ATS President James Lamb, Ph.D., wrote, "This honor represents a significant milestone in the development of your career in toxicology. You have earned this recognition following a thorough review of your scientific credentials by your peers."

According to its online history, ATS was established in 1981, to assure the objective and unbiased understanding and interpretation of toxicity data developed for the protection of public health. With its emphasis on peer review and regulatory toxicology, certification by ATS is complementary to, but distinct from, certification as a Diplomate of the American Board of Toxicology (DABT).

NIEHS/NTP Director Linda Birnbaum, Ph.D., a DABT since 1982, and a fellow of ATS since 2006, welcomed Stokes to the academy. "This is an impressive addition to Bill's other certifications and honors," she said, "and a credit to NTP's alternative testing programs. I offer Bill my sincere congratulations on this honor."

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NTP Research Fellow gains toxicology certification

In Ok Surh
(Photo courtesy of Steve McCaw)

In November, In Ok Surh, Ph.D. was awarded certification of Diplomate of the American Board of Toxicology (DABT) after much hard work and dedication. Surh is a Research Fellow in the applied toxicology and carcinogenesis program of the Toxicology Branch of the Division of the National Toxicology Program. Currently, she leads several projects that involve herbal medicines, chemical intermediates, and environmental contaminants. Surh received a B.S. in pharmacy and a M.S in hygienic chemistry from Duksung Women's University, Korea. She is a licensed pharmacist in Korea and holds a Ph.D. in pharmacy from the University of Texas at Austin, Texas.

The American Board of Toxicology was established in 1979 to advance standards in the field of toxicology and confer recognition upon those members of the profession who, measured against such standards, demonstrate competence. DABT certification requirements include a combination of education and experience and a three-part examination.

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NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

NICEATM holds workshop on new safety tests for pertussis vaccines

Excerpted from *eFACTOR*, January 2013 article by Debbie McCarley and Cathy Sprankle

Stokes, front right, joined more than 40 scientists from 11 countries representing vaccine manufacturers and government regulatory agencies at the November 2012 workshop. (Photo courtesy of NICEATM)

NIEHS and U.S. Food and Drug Administration (FDA) scientists joined other experts from around the world at a workshop to consider improved methods and approaches for safety testing of vaccines that protect against pertussis. The "International Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines: State of the Science and the Path Forward" was held Nov. 28-29, 2012, at the William H. Natcher Conference Center on the NIH campus in Bethesda, MD.

The workshop provided a forum for participants to review protocols and available data from an ongoing international study of *in vitro* alternatives for safety testing of pertussis vaccines. The workshop participants also considered the next steps to achieve validation, global acceptance, and implementation of these test methods.

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) organized the workshop in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and partner organizations of the International Cooperation on Alternative Test Methods.

A more detailed summary of the workshop and speaker presentations are available on the ICCVAM website. A report on the workshop will be appear later this year in the journal Biologicals.

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NICEATM workshop reviews new *Leptospira* vaccine testing approaches

Excerpted from *eFACTOR*, December 2012 article by Debbie McCarley and Cathy Sprankle

The organizing committee for the *Leptospira* workshop, gathered for a photo after the workshop. From left to right, Marta Guerra, D.V.M., Ph.D., Centers for Disease Control and Prevention; Eric Klaasen, D.V.M, Ph.D., MSD Animal Health, The Netherlands; Jeffrey Galvin, Ph.D., Pfizer Animal Health; Brett Webster, Boehringer Ingelheim Vetmedica, Inc.; David Alt, D.V.M., Ph.D., USDA; Karen Brown, Ph.D., Pair O Docs Consultants; Hans Draayer, Gourdneck View Consulting, LLC; Catrina Stirling, Ph.D., Pfizer; Warren Casey, Ph.D., NICEATM; Geetha Srinivas, D.V.M, Ph.D., USDA; Angela Walker, D.V.M, Ph.D., USDA; Stokes; Kevin Ruby, Ph.D., USDA; Randal Sebring, D.V.M., Colorado Serum Company; Richard McFarland, M.D., Ph.D., FDA (Photo courtesy of James Fosse, USDA)

Later in September, over 80 scientists from around the world gathered in Ames, Iowa, at the NICEATM-sponsored "International Workshop on Alternative Methods for *Leptospira* Vaccine Potency Testing: State of the Science and the Way Forward." Workshop participants reviewed available improved methods for *Leptospira* vaccine potency testing, which currently uses many laboratory animals and causes significant pain and distress to the animals used.

Participants in the workshop, including vaccine manufacturers and regulators, discussed steps that could be taken to achieve wider use of *in vitro* replacement methods for *Leptospira* vaccine potency testing developed by the U.S. Department of Agriculture (USDA) Center for Veterinary Biologics. These suggestions included exploration of new approaches to validation, and sharing of data, reagents, and best practices.

Slides presented by speakers are available on the NICEATM website. A workshop report will be published next year as a special issue of the journal Biologicals.

(Debbie McCarley is a special assistant to Stokes. Cathy Sprankle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

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New OECD Test Guidelines Available for Endocrine Disruptor Testing

OECD has also officially adopted two test guidelines for test methods to identify substances with the potential to affect the function of the endocrine system. Both test guidelines describe *in vitro* methods that do not use animals, and the tests are appropriate for use in the U.S. Environmental Protection Agency (EPA) Endocrine Disruptor Screening Program.

Test Guideline 457 describes the BG1Luc estrogen receptor (ER) transactivation (TA) assays to detect ER agonist and antagonists and provides performance standards for each assay. The test guideline was based on data from an international validation study that was coordinated by NICEATM in conjunction with JaCVAM and ECVAM and that included laboratories in the United States, Japan, and Italy.

NICEATM worked closely with the EPA to conduct this method through the OECD nomination and adoption process. The adoption of Test Guideline 457 means that these methods may now be used in the 34 member countries of the OECD. In July 2012, the EPA announced its acceptance of the BG1 method as an alternative to the HeLa9903 TA assay in response to a recommendation by ICCVAM.

The existing Test Guideline 455 has been updated to include both the BG1 and HeLa9903 methods, and now describes general characteristics of stably transfected transactivation *in vitro* assays to detect ER agonists. This performance-based test guideline also provides standards that will support more efficient validation of new test methods of this type. These standards include a harmonized list of reference chemicals that should be tested during assay development, as well as performance standards that should be met by successful assays.

The new test guidelines are available on the ICCVAM website:
OECD Test Guideline 457: "BG1Luc Estrogen Receptor Transactivation Test Method for Identifying Estrogen Receptor Agonists and Antagonists" is available at http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/OECD/OECD-TG457-508.pdf

OECD Test Guideline 455: "Performance-Based Test Guideline for Stably Transfected Transactivation *In Vitro* Assays to Detect Estrogen Receptor Agonists" is available at http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/OECD/OECD-TG455-2012-508.pdf. ●

Contact Information: Warren Casey, Ph.D., Acting Director, NICEATM, NIH/NIEHS, P.O. Box 12233, MD K2-16, Research Triangle Park, NC 27709; T: 919-316-4729; FAX: 919-541-0947; niceatm@niehs.nih.gov

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In Memorial

Hart flashed his characteristic smile during his retirement party in 1999. (Photo courtesy of Steve McCaw)

NTP is sad to announce that Larry Hart, Ph.D. passed away October 22, 2012, following complications from a fall. Dr. Hart attended the University of Iowa in Iowa City, earning a B.S. in pharmacy in 1960 and a Ph.D. in pharmacology in 1964. He retired in 1999 after 30 years of service with NIH, NIEHS, and NTP. At the time of his retirement, he was serving, among other scientific efforts, as executive secretary of the NTP Board of Scientific Counselors. Dr. Hart was remembered with fondness and praise by former colleagues and friends at a memorial service on November 2 in Chapel Hill, NC.

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The NTP website offers electronic files of the Report on Carcinogens and the library of NTP Technical Reports and NTP Toxicity Reports. The PDF files of these reports are available free-of-charge through the NTP website at http://ntp.niehs.nih.gov (see Resources).

Contact Information: NTP Office of Liaison, Policy and Review, NIEHS, P.O. Box 12233, MD K2-03, Research Triangle Park, NC 27709; T: (919) 541-0530; FAX: (919) 541-0295; CDM@niehs.nih.gov

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