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

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National Institute of Environmental
Health Sciences • NIH-HHS

New NTP atlas helps standardize nonneoplastic lesion diagnoses

By Robin Mackar, reprinted from Environmental Factor, February 2014

In January, NTP debuted a new web-based resource that will help pathologists worldwide better diagnose, record, and discuss nonneoplastic rodent lesions. Nonneoplastic lesions, or noncancer lesions, can be precursors to cancer and can also be associated with life-threatening, noncancerous diseases, such as pulmonary fibrosis, and are therefore important findings in toxicity and carcinogenicity studies.

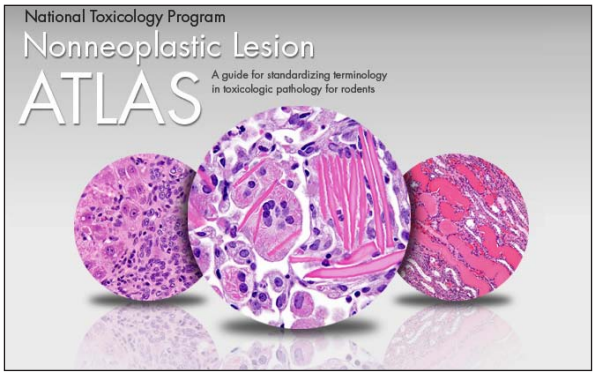
This new tool, the NTP Nonneoplastic Lesion Atlas, is available online and is highlighted in a new commentary by NTP staff in the peer-reviewed journal Toxicologic Pathology.

When completed, the Atlas will consist of thousands of high-quality, zoomable images and diagnostic guidelines arranged in 56 sections organized by organ system, each covering a particular organ or tissue. The subsections on bone marrow in the hematopoietic system; liver and gallbladder in the hepatobiliary system; skin in the integumentary system; brain, nerve, and spinal cord in the nervous system; and the ureter and urinary bladder in the urinary system section are already available.

In addition to the digital images, each lesion page includes the NTP recommended terminology, histopathologic descriptions, and other useful information about the lesions, diagnostic guideline recommendations, and references.

NTP Nonneoplastic Lesion Atlas: A New Tool for Toxicologic Pathology

Read more about the NTP Nonneoplastic Lesion Atlas in Environmental Health Perspectives, March 2014



The NTP Nonneoplastic Lesion Atlas was the brainchild of Sills. It will be used by NTP and its many pathology partners to standardize lesion diagnosis, terminology, and the way lesions are documented. It is expected to improve understanding, consistency, and accuracy between pathologists and laboratories. (Photo courtesy Steve McCaw)

An authoritative resource

"Having a resource that toxicologists and pathologists all over the world can use to speak the same language when diagnosing nonneoplastic lesions in rats and mice will be invaluable to the NTP and to the field," said Robert Sills, D.V.M., Ph.D., head of the NTP Cellular and Molecular Pathology Branch.

Sills conceived the atlas and, along with his team, helped bring the project to fruition. "Being able to actually zoom in and see, in exquisite detail, what these lesions look like and knowing the preferred NTP diagnostic term for each lesion will lead to more standardization of study results," he explained.

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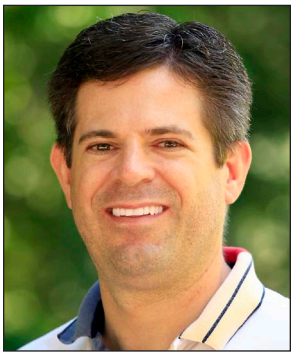

Cesta has been instrumental in reviewing and coordinating all the content for the new atlas, and has worked with a dedicated team of federal and contract staff to bring the atlas to fruition. When completed, the atlas will contain 56 sections and thousands of images. (Photo courtesy Steve McCaw)

The images have been compiled mostly from the NTP archives, a state-of-the art facility that the NTP has been supporting since 1984 to house its expansive collection of research specimens and supporting data from NTP studies.

"The pathology community looks to NTP to develop these kinds of resources," Sills said. The atlas helps improve the organization and diagnostic consistency of the NTP database and can also be used by other laboratories to standardize their diagnostic strategy and improve their own databases.

Establishing the gold standard

"The NTP has long been known for establishing the diagnostic criteria and terminology for neoplastic lesions in rodent cancer bioassays and we wanted to establish the same standards for nonneoplastic lesions," said NTP pathologist Mark Cesta, D.V.M., Ph.D., an editor and author of the Toxicologic Pathology paper and the atlas. Cesta adds that nonneoplastic diseases are also a major cause of morbidity and mortality in humans, with some of these diseases thought to be brought on by environmental causes, making this resource valuable to medical researchers worldwide, as well as to NTP study pathologists.

"We know that many lesions seen in human diseases have relevant counterparts in NTP rodent toxicity and cancer studies," Cesta said. "This will be a living document that we will keep updating as new information about diagnosing nonneoplastic lesions becomes available," Sills said. "It will become the must-have resource for every pathologist and a great training tool for the next generation of toxicologic pathologists."

Collaborative effort

"This was truly a group effort," said NTP Associate Director John Bucher, Ph.D. "We couldn't have accomplished this without drawing upon the expertise of many." Each section of the Atlas was extensively reviewed by NTP pathologists and by independent pathology experts who specialize in specific organ systems.

Additionally, experts in web-based technologies were also called upon to create the online searchable database. The Atlas also went through several focus groups before launching to ensure usability. "I think the Atlas will be a tremendous resource to the NTP and many others," Bucher added.

NTP is proactively creating awareness about the Atlas among key stakeholders. The NTP will host an exhibitor session at the Society of Toxicology annual meeting in March, offer demonstrations during a NTP satellite symposium at the Society of Toxicologic Pathology annual symposium in June, and provide several demonstrations and webinars for NIEHS and NTP staff, grantees, international users, and pathology students, among others.

Citation: Cesta MF, Malarkey DE, Herbert R, Brix A, Hamlin M, Singletary E, Sills RC, Bucher JR, Birnbaum LS. 2014. The National Toxicology Program web-based Nonneoplastic Lesion Atlas: A global toxicology and pathology resource. Tox Path 42:458-460.

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison, and a frequent contributor to the Environmental Factor.)

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Upcoming NTP Events

April 16-18, 2014

NTP Board of Scientific Counselors

This meeting was postponed from December 18-19, 2013

http://ntp.niehs.nih.gov/go/165

May 5-6, 2014

ICCVAM Workshop

Collaborative Workshop on Aquatic Models and 21st Century Toxicology

Location: James B. Hunt Jr. Library, North Carolina State University, Raleigh, NC

http://ntp.niehs.nih.gov/go/41308

May 22, 2014

NTP Technical Reports Peer Review Meeting

http://ntp.niehs.nih.gov/go/36051

June 17-18, 2014

NTP Board of Scientific Counselors

http://ntp.niehs.nih.gov/go/165

August 12, 2014 *(tentative)*

NTP Board of Scientific Counselors

Peer Review of Draft Report on Carcinogens (RoC) Monograph on Trichloroethylene (TCE)

http://ntp.niehs.nih.gov/go/38853

September 16-17, 2014

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

http://ntp.niehs.nih.gov/go/32822

December 9-10, 2014

NTP Board of Scientific Counselors

http://ntp.niehs.nih.gov/go/165

All meetings are held at NIEHS unless otherwise noted:

Rodbell Auditorium
NIEHS
111 TW Alexander Drive
Research Triangle Park, NC 27709

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

World Health Organization and NIEHS launch new collaboration

By Paula Whitacre, reprinted from Environmental Factor, March 2014

Whether at breakfast, a roundtable discussion, or the Collaborating Centre launch itself, Neira shared her commitment to preventing adverse environmental impacts on health. (Photo courtesy of Steve McCaw)

NIEHS and the World Health Organization (WHO) began a new chapter in their decades-long partnership Feb. 20, with the official launch of the NIEHS-WHO Collaborating Centre for Environmental Health Sciences. NIEHS welcomed Maria Neira, M.D., director of the WHO Public Health and Environment Department, as keynote speaker. The event took place in conjunction with the winter meeting of the National Advisory Environmental Health Sciences Council.

"By joining forces, NIEHS and WHO will help to ensure that cutting edge environmental health science will be translated into effective public health interventions to improve health around the world," said NIEHS and NTP Director Linda Birnbaum, Ph.D.

Building bridges

As a WHO Collaborating Centre, NIEHS joins a network of academic and scientific institutions around the world dedicated to information exchange and technical cooperation.

"Even as the global health community shifts its focus from infectious to non-communicable diseases, the critical role of environmental exposures in adding to the global chronic disease burden is not well appreciated. The Collaborating Centre provides a new and unique platform for NIEHS to address this gap in awareness," said John Balbus, M.D., NIEHS senior advisor for global health and head of the new center.

WHO is the United Nations authority for directing and coordinating global health promotion efforts. It is responsible for providing leadership on health matters, shaping the research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries, and monitoring and assessing health trends.

WHO operates six regional offices, with Collaborating Centres located in more than 80 countries. The member states of WHO comprise most countries of the world, providing an extensive network of health experts and health ministries that the Collaborating Centres can access for research translation and communication. In addition to working directly with WHO, the centers collaborate with each other in formal and informal networks on topics ranging from adolescent health to zoonoses (diseases and infections that are naturally transmitted between vertebrate animals and humans).

NIEHS focus

The Collaborating Centre at NIEHS will focus on five priorities for research and research translation – children's environmental health, climate change and human health, developmental origins of health and disease, e-waste, and indoor air pollution. "Increased dialogue and understanding is a benefit to being a Collaborating Centre," said Claudia Thompson, Ph.D., a member of the NIEHS Global Environmental Health Program Steering Committee. "The designation also will increase integration across common themes within the Institute."

For example, NIEHS seeks to better understand the link between indoor air pollution and premature deaths, such as through support of intervention studies to investigate realistic alternatives to biomass-burning cookstoves in developing countries. "Having the weight of being a Collaborating Centre, we can see who else has activities in this area around the globe, which should help in coordination and more quickly getting data," Thompson said. "That will help increase dialogue and accelerate findings."

The collaboration

The Collaborating Centre designation culminates three productive decades of partnership, beginning with a cooperative agreement in the early 1980s, facilitated by William Suk, Ph.D., director of the NIEHS Center for Risk and Integrated Sciences and the Superfund Research Program.

As detailed in a 2011 WHO publication, cooperation between the two agencies helped further the International Programme on Chemical Safety and the Environmental Criteria series. With more than 200 peer-reviewed publications, this influential series provides information on a range of environmental health topics to governments.

As a Collaborating Centre, the two organizations will continue to work together to develop training programs, and support and host conferences and workshops related to its five focus areas.

(Paula Whitacre is a contract writer with the NIEHS office in Bethesda, MD.)

Highlights from the Society of Toxicology Meeting March 23-27, 2014, Phoenix, AZ

At the MOU signing ceremony, Nigel Walker, Ph.D., of NTP, center, joined with Birnbaum, left, and Dori Germolec, Ph.D., who is an SOT Counselor. (Photo courtesy of Robin Mackar)

Cesta, left, showed many people, including fellow NTP toxicologist Scott Auerbach, Ph.D., the capabilities of the new NTP Nonneoplastic Lesion Atlas. (Photo courtesy of Robin Mackar)

Memorandum of understanding

A memorandum of understanding (MOU) between SOT and NIEHS was signed which set forth a framework for collaborations to provide global leadership toward creating a safer and healthier world, by increasing the impact of the science of toxicology.

Exhibitor hosted session

Mark Cesta, D.V.M., Ph.D., showcased the Nonneoplastic Lesion Atlas, the newest resource from NTP.

SOT Awards

First Place for the Drug Discovery Toxicology SS Emil A. Pfitzer Postdoctoral Award

Rachel Goldsmith, Ph.D., Fellow, Biomolecular Screening Branch

Best Abstract Award from the SOT Mixtures Specialty Section

Kembra Howdeshell, Ph.D., Office of Health Assessment and Translation

Third Place Postdoctoral Award in the Metals Specialty Section

Katie Pelch, Ph.D., Fellow, NTP Laboratory

Stem Cell Specialty Section Postdoctoral Award for Research Excellence

Olive Ngalame, Ph.D., Fellow, NTP Laboratory

Best Publication Award in the Nanotoxicology Specialty Section

Brian Sayers, Ph.D., Fellow, Toxicology Branch

Seminar explores communication of uncertainty and risk

By Kelly Lenox, reprinted from Environmental Factor, April 2014

Objectivity is the touchstone for scientists of every discipline. But when civic responsibility calls for decision making in the context of uncertainty, as it does for scientists in NTP, researchers must grapple with how to effectively communicate their findings.

For insight into how to better express conclusions on potential health concerns associated with exposure to environmental substances, NTP turned to two experts in psychology – David Budescu, Ph.D., of Fordham University, and Thomas Wallsten, Ph.D., of the University of Maryland (UM). Budescu and Wallsten discussed this issue at a seminar March 11 at NIEHS.

For NTP, an important part of reviewing literature-based health assessments (see story) involves examining how to best communicate the results of those assessments, according to Kristina Thayer, Ph.D., director of the NTP Office of Health Assessment and Translation. NTP stakeholders include decision-makers in the public and private sectors, as well as individuals with concerns about their own environmental health.

A concern with levels of concern

"When the literature base is well developed, it can result in a formal NTP conclusion referred to as a level of concern (LOC), which integrates what is known about health hazard with the extent of human exposure," Thayer said.

LOC conclusions are narrative rather than quantitative, and that has resulted in some confusion, Thayer continued. "For example, researchers and the public have expressed difficulty in distinguishing between a substance being of 'some concern' and being 'of concern,'" she explained.

Mary Wolfe, Ph.D., director of the NTP Office of Liaison, Policy and Review, further detailed the challenge of LOC terms. "Do we have too many categories? Should we use numbers along with the words?" she asked. "It's about how we frame the outcome of an evaluation."

Use both verbal and numerical terms

"Decision-makers are best served when the terms used in communicating uncertainty match the ambiguity of the event and the uncertainty of its occurrence," said Budescu (see text box on right).

As an example of ways to better deal with ambiguity, he pointed to an international study on communicating uncertainty about climate change. In 25 countries, researchers compared the understanding of two forms of conveying uncertainty – verbal terms, and verbal combined with numerical terms. The verbal terms, such as "very likely," were linked to a separate table listing the numerical value of that likelihood. The verbal combined with numerical terms, such as "very likely (greater than 90 percent probability)," included the numerical value alongside.

Researchers were surprised that, even though a reference table of values was provided, understanding of the verbal terms alone

Budescu is a professor of psychometrics and quantitative psychology at Fordham University. (Photo courtesy of Steve McCaw)

Wallsten is a professor emeritus in the department of psychology and senior scientist at the UM Center for Advanced Study of Language. (Photo courtesy of Steve McCaw)

Distinguishing sources of uncertainty

Budescu categorized three sources of imprecision when communicating probability.

- The ambiguity of the event itself – for example, "drawing a queen from a deck of cards" is a less ambiguous event than "a drop in the market in the near future."
- The type of uncertainty, or the degree to which the probability of an event can be quantified – for example, "34 percent more likely" is more precisely quantified than "more likely."
- The language of communication – for example, "drop 6 cents per share" is more precise than "drop 10 to 20 percent in value."

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varied considerably among readers. "The presentation of verbal with numerical information achieves better understanding of the terms," Budescu said, noting that understanding improved both across countries surveyed and across all terms used.

Obtain and encode expert judgment

Wallsten discussed a process for obtaining and communicating expert judgment – another technique for communicating risk in cases of inadequate data. He outlined an example in which a small panel of 5-7 highly respected scientists was selected using an open and transparent process. The preparation of panel members included enhancing their sensitivity to sources of uncertainty.

The process included numerically encoding the subjective judgments of the expert panel, for example, the likely dose-response rates after exposure to an air pollutant. "Encoding the judgment calls can be useful in representing the extent of consensus or disagreement among the experts," said Wallsten. This step echoed Budescu's finding of the importance of using numerical values when communicating uncertainty.

"Subjectivity cannot be avoided, but it can be translated to a level of concern via an open and principled process," Wallsten concluded.

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Webinar advances review of TCE

By Ernie Hood, reprinted from Environmental Factor, April 2014

Lunn provides scientific expertise for the overall evaluation of substances for their potential to cause cancer in humans. (Photo courtesy of Steve McCaw)

The National Toxicology Program (NTP) sought input from the public March 17, as it prepared to write a draft monograph on its review of trichloroethylene (TCE). Cheryl Siegel Scott, of the U.S. Environmental Protection Agency, moderated the four-hour webinar, which attracted more than 75 participants.

TCE was first listed as reasonably anticipated to be a human carcinogen in the 9th Report on Carcinogens (RoC), issued in 2000. A listing in the RoC does not, by itself, mean that a substance will cause cancer. Many factors, including the amount and duration of exposure, as well as an individual's susceptibility to a substance, play a role in whether a person will develop cancer or not.

New studies lead to reconsideration

TCE is a halogenated alkene used primarily as a metal degreaser, with both occupational and environmental exposures. "Since the last review in 2000, there have been several additional human cancer studies published, so we are going to rereview TCE for possible change in its RoC listing status," said Ruth Lunn, Dr.P.H., director of the Office of the Report on Carcinogens.

The specific purpose of the webinar was two-fold – to gain external scientific input on issues related to the assessment of information on exposure and cancer outcomes in epidemiologic studies of TCE, and to obtain public input on the protocol for preparing the draft RoC monograph on TCE.

Exposure assessment quality

Patricia Stewart, Ph.D., a consultant with Stewart Exposure Assessments, LLC, in Arlington, Va., reported the results of her systematic evaluation of the quality of exposure assessments in TCE epidemiologic studies.

Stewart rated the cohort and case-control studies according to several criteria, including occupational measures, exposure assessment methods used, and types of exposure estimates and metrics employed. She also evaluated the studies in terms of likelihood and intensity of exposure.

Cancer outcome classification

Bernard Goldstein, M.D., from the University of Pittsburgh, spoke about methods used to classify cancer outcomes, specifically lymphohematopoietic cancers.

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He cautioned that, particularly in the case of non-Hodgkin lymphoma (NHL), although recent advances and changes in classification of neoplasm subtypes enhance treatment choices, they complicate establishment of direct cause-and-effect relationships between specific chemicals and one of the subtypes of NHL.

According to Goldstein, the classification of subtypes should not preclude grouping of subtypes in certain circumstances. "Is it appropriate to combine cancer incidence of different lymphoid tumors in an epidemiological study or meta-analysis?" he asked. "I happen to think it is."

TCE epidemiological studies

National Cancer Institute (NCI) researcher Mark Purdue, Ph.D., reported on the use of exposure and outcome assessments in TCE epidemiologic studies. He described the various methods used in exposure assessment studies and provided his opinions about which were the best, largely based on how quantitative the measurements were. "When evaluating evidence from cohort and case-control studies of TCE, it's essential to consider the quality of exposure assessment," he noted.

According to Purdue, imperfect exposure sensitivity and specificity can introduce misclassification, which would generally bias toward the null, especially when measuring rare exposures such as TCE.

Public input

Following the three presentations, the speakers, NTP staff, and members of the public engaged in a discussion, providing further input on the scientific issues that were raised. Neela Guha, Ph.D., of the International Agency for Research on Cancer (IARC) led the discussion, posing a series of questions to the speakers in four specific areas – exposure metrics and surrogates, and coexposures; exposure levels and response; exposure misclassification and its effects on epidemiological observations; and disease classification of hematological cancers.

Next steps

Lunn noted that the webinar's proceedings would help her group write the cancer evaluation component of the draft monograph. "When that is finished," she said, "we will post it on our website for public comment, and then we plan to hold a peer review meeting for the draft monograph." ●

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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International collaboration aims to reduce animal testing

By Catherine Sprankle, reprinted from Environmental Factor, February 2014

A researcher operates a staining platform in the high-throughput screening facility at IHCP. Attendees at the ICATM meeting had an opportunity to tour facilities used to conduct high-throughput screening experiments. (Photo courtesy of the Institute for Health and Consumer Protection)

Governments around the world require chemical and chemical product testing to identify potential hazards, so that appropriate labeling for safe handling, use, and disposal may be applied. The U.S. shares an interest with other countries to discover more efficient testing methods that reduce or eliminate animal use.

The International Cooperation on Alternative Test Methods (ICATM), a partnership promoting the replacement, reduction, and refinement of alternatives for animal testing, met Nov. 26-27, 2013 at the European Commission Institute for Health and Consumer Protection (IHCP) in Ispra, Italy. NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) Director Warren Casey, Ph.D., represented the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) at the meeting. NICEATM provides support for ICCVAM activities, and Casey is an ICCVAM committee member.

"This was an extremely productive meeting," notes Casey. "The attendees reached some agreements that should facilitate U.S. regulatory agencies' adoption of methods that have undergone peer review outside the United States, which will result in more efficient testing and less animal use."

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Advancing international adoption of alternative test methods

ICATM facilitates international cooperation in validation, peer review, and development of recommendations on use of new test methods. Casey and the other participants at the meeting made some key decisions to support those goals, including the following agreements.

- Use of the European TSAR (Tracking System for Alternative test methods Review, Validation and Approval in the Context of EU Regulations on Chemicals) as the common tracking database for new test methods developed by ICATM partners.
- The need to define best practices for validation study activities, such as chemical selection, the composition and role of study management teams, and consideration of international classification systems.
- The need to establish and adhere to best practices for compiling data from traditional animal studies for use in validation of new methods, with NICEATM skin sensitization and endocrine disruptor databases to serve as trial cases.

In addition to the procedural discussions, the November meeting included updates on current test method evaluation and validation activities in Europe, Japan, Korea, and the U.S.

Casey provided two updates on U.S. activities. One focused on the reinvention of ICCVAM, as outlined by NIEHS and NTP Director Linda Birnbaum, Ph.D. (see story).

The other summarized recent NICEATM and ICCVAM activities, including evaluations of acute toxicity and eye safety tests; a workshop focused on reduction and replacement of animal use for *Leptospira* vaccine testing; and activities supporting Tox21 and development of high-throughput screening tests. Attendees at the meeting also had the opportunity to tour the Joint Research Centre's Good Laboratory Practice facility used to conduct high-throughput screening experiments.

ICATM currently includes member organizations from the European Union, U.S., Japan, Canada, and South Korea. ICATM coordination meetings take place several times a year and provide an opportunity for the five member organizations to discuss activities in their major areas of cooperation. Regular interactions allow the ICATM partners to develop good communications and working relationships, which support collaborations on test method development.

(Catherine Sprankle is a communications specialist with ILS Inc., support contractor for NICEATM.)

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NTP presentations highlight new technologies to protect human health

By Catherine Sprankle, reprinted from Environmental Factor, March 2014

New technologies like high-throughput and high-content screening generate large amounts of data on potential toxic effects of chemicals. However, making sense of the data and using it to predict the effects of chemicals on human health remain a challenge. Over 20 NIEHS and NTP scientists joined nearly 300 researchers Jan. 16-17 at the University of North Carolina at Chapel Hill Friday Center to address this challenge.

"FutureTox II: *In Vitro* Data and *In Silico* Models for Predictive Toxicology" brought together experts in computational and high-throughput non-animal toxicology methods. The goal of the conference was to consider how these new technologies could lead to faster, cheaper, and more relevant alternatives to animal testing, to assess the potential toxic effects of chemicals.

NIEHS and NTP presenters discuss alternative toxicity data

Plenary sessions focused on biological systems, predictive models, and regulatory integration and communication. Among the presenters in the session on predictive models were NIEHS Deputy Director Richard Woychik, Ph.D., and Scott Auerbach, Ph.D., of the NTP Biomolecular Screening Branch.

Woychik focused on using stem cells derived from outbred mouse populations as a model for identifying variations in toxicity among humans. Auerbach discussed the use of gene expression data, from cells treated with chemicals that have known toxic effects, to predict possible toxic effects of related chemicals that are lacking toxicity data.

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Alternatives for endocrine disruptor and skin sensitizer identification

NTP scientists presented 10 posters at the Jan. 16 poster session. Of these, five from the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) addressed ongoing projects to develop alternative methods for identifying potential endocrine disruptors and skin sensitizers. Other posters were presented by members of NTP's Biomolecular Screening Branch and Toxicology Branch.

A poster by Nicole Kleinstreuer, Ph.D., contractor for NICEATM, outlined an approach that uses data from the EPA ToxCast research program to identify potential skin sensitizers. "The poster session was well-attended. The research presented on the posters was very timely and relevant to the goals of the meeting and generated some lively discussions." Kleinstreuer commented. "Overall, this was a very informative and productive meeting."

Strategies for application of new methodologies

Following the plenary and poster sessions, conference participants attended breakout groups to discuss strategies for applying the testing approaches to areas of current interest. The four breakout discussions focused on regulatory toxicology, liver toxicity, cancer, and developmental and reproductive toxicity.

Conference organizers will prepare an article on the outcomes of the meeting, for submission to the Forum section of the journal Toxicological Sciences later this year. Also, conference attendees will be invited to contribute manuscripts on conference topics to a special issue of Reproductive Toxicology.

(Catherine Sprankle is a communications specialist with ILS Inc., support contractor for NICEATM.)

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Collaboration, focus, and innovation keys to replacing animal use

By Catherine Sprankle, reprinted from Environmental Factor, April 2014

Casey noted that increasing NTP leadership and direction for ICCVAM will better support the acceptance and use of testing methods that reduce or replace animals. (Photo courtesy of Thomas Leach, New Jersey Association for Biomedical Research)

Warren Casey, Ph.D., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), delivered the keynote address at a Feb. 27 gathering of researchers and regulators in Somerset, N.J.

The 3Rs Sharing Conference, "Paving the Path to Regulatory Acceptance of Alternative Methods: Facilitating the Integration of Alternative Methods Into the Regulatory Framework," included speakers from the pharmaceutical and chemical industries presenting case studies and strategies for effective safety testing using fewer animals. The New Jersey Association for Biomedical Research (NJABR) sponsors the annual conference.

Evolution of NTP and interagency alternative methods programs

Casey's keynote, "New Direction and Transformation of NICEATM and ICCVAM," addressed recent changes in NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which NICEATM supports. He outlined how these changes will allow ICCVAM to use limited resources more effectively, leverage the efforts of international partners, and take advantage of innovations in toxicological science.

He also discussed ICCVAM's advisory role and emphasized that collaboration and coordination will be important to future success. "Considering ICCVAM's limited resources, the projects the committee takes on need to be those most likely to lead to real reductions in animal use, in areas such as vaccine testing, acute toxicity testing,

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and identification of skin sensitizers," Casey noted. "But if ICCVAM collaborates and communicates effectively with its international partners and other stakeholders, the efforts of those partners can support ICCVAM's progress towards its goals."

In the past, NICEATM focused primarily on providing support to ICCVAM. Recently, NICEATM became active in the interagency Tox21 collaboration, of which NTP is a partner. "NICEATM's expertise in validation study design and data analysis will help Tox21 achieve its goals of developing predictive toxicological models and reducing reliance on animal testing," said Casey.

(Catherine Sprankle is a communications specialist with ILS Inc., support contractor for NICEATM.)

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

NICEATM makes statistical tools available to identify potential skin sensitizers

Skin sensitizers are substances with the potential to cause allergic contact dermatitis; traditional testing methods to identify skin sensitizers use animals. Regulatory requirements and concerns about testing efficiency and animal welfare are driving efforts to replace traditional testing methods with nonanimal methods. NICEATM is collaborating with NTP statisticians and scientists at Procter and Gamble (P&G) in Brussels, Belgium, to create an integrated testing strategy to identify potential skin sensitizers without using animal tests.

In practice, it usually takes several nonanimal tests to provide the same level of information as single animal test. An integrated testing strategy developed by P&G uses a Bayesian network to analyze all available relevant substance information, including nonanimal tests, *in silico* models, and other information such as chemical structure and solubility, to produce a numerical probability of skin sensitization potency. Using the available information, the Bayesian network can indicate the next test to perform that will add the most information to the skin sensitization potency prediction for a substance. The calculated probability could be used to make hazard labeling decisions without animal testing. The software used by P&G for these analyses is proprietary; the goal of the NICEATM collaboration was to develop similar tools using the R software package to make the integrated testing strategy approach more widely usable.

Downloadable files to run the analysis, along with documentation and sample data, are available at http://ntp.niehs.nih.gov/go/its. A user community and listserv is being formed to encourage collaboration on improvement and refinement of integrated testing strategies for skin sensitizers. On NICEATM's website are data available as reference material to use in evaluating alternative methods for skin sensitization testing (http://ntp.niehs.nih.gov/go/40498).

ICCVAM elects chairs

ICCVAM is an interagency committee of representatives from 15 U.S. Federal regulatory and research agencies that generate or use toxicological and safety testing information. At ICCVAM's January meeting, the ICCVAM agencies' principal representatives elected Abby Jacobs, Ph.D., of the FDA and Anna Lowit, Ph.D., of the EPA to serve as co-chairs of ICCVAM for the coming year. Jacobs and Lowit served as acting co-chairs of ICCVAM during 2013 and will continue to lead ICCVAM as it defines new procedures and sets goals and priorities for the near future.

Upcoming workshops on alternatives

A "Collaborative Workshop on Aquatic Models and 21st Century Toxicology" will be held May 5–6 at the Hunt Library at North Carolina State University in Raleigh, NC. The purpose of the workshop will be to explore and discuss how aquatic models may be used to (i) screen and prioritize compounds for further *in vivo* testing and (ii) assess mechanisms of chemical toxicity and how this knowledge can impact the environment and human health. Information about the workshop is available at http://ntp.niehs.nih.gov/go/41308.

A workshop on "Adverse Outcome Pathways: From Research to Regulation" will be held September 3–5 in the William H. Natcher Conference Center, National Institutes of Health, Bethesda, Md. Information and a registration form for this workshop will be available on the NTP website in the near future.

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