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

October 2014

Headquartered at the
National Institute of Environmental
Health Sciences • NIH-HHS

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NAS agrees with NTP Report on Carcinogen listing decisions

By Robin Mackar, reprinted from Environmental Factor, September 2014

New reports from the National Academy of Sciences (NAS) find that the National Toxicology Program (NTP) listings of styrene and formaldehyde, in the 12th Report on Carcinogens (RoC) published in 2011, are accurate and appropriate.

Ruth Lunn, Dr.P.H., director of the NTP Office of the Report on Carcinogens, along with her staff and NTP leadership, ensures a rigorous scientific review process for all NTP evaluations. (Photo courtesy of Steve McCaw)

The separate reports were developed after Congress directed the U.S. Department of Health and Human Services (HHS) to arrange for NAS to independently review the 12th RoC substance profiles of styrene and formaldehyde. NAS began work in September 2012.

The RoC is a science-based document that identifies cancer hazards. It is a cumulative report, prepared by NTP on behalf of the HHS Secretary.

"We appreciate the efforts of these two committees, convened by the NAS, and are very pleased with these supportive outcomes," said NIEHS and NTP Director Linda Birnbaum, Ph.D.

Styrene

The NAS committee that reviewed the styrene assessment in the 12th RoC released its final report July 28.

After conducting both a peer review and an independent assessment of the styrene literature, the committee found that the overall conclusion reached by NTP in 2011, that styrene is reasonably anticipated to be a human carcinogen, is appropriate.

Styrene is an industrial chemical used to reinforce plastic and rubber products. The listing of styrene in the RoC was based on levels of styrene that workers are exposed to in an industrial setting.

Formaldehyde

A separate NAS committee focused on formaldehyde. Their final report, released Aug. 8, upheld the 12th RoC listing of formaldehyde.

The committee agreed with the NTP determination that evidence from studies in humans for nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia was sufficient to support listing formaldehyde as a known human carcinogen.

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As with the styrene report, the committee conducted both a peer review of the NTP formaldehyde assessment and an independent assessment of the literature.

Formaldehyde is a major industrial chemical used in building materials, chemical manufacturing, and other industries.

Well-placed public trust

"The Report on Carcinogens has always had a high level of public trust," said NTP Associate Director John Bucher, Ph.D. "These two reports from the National Academy of Sciences confirm that public trust and confidence in NTP's rigorous scientific review process is well-placed."

Several of the recommendations made by the committee have already been put in place, as NTP continues reviewing candidate substances for possible listing in the RoC.

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

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NTP to conduct testing on chemicals from West Virginia spill

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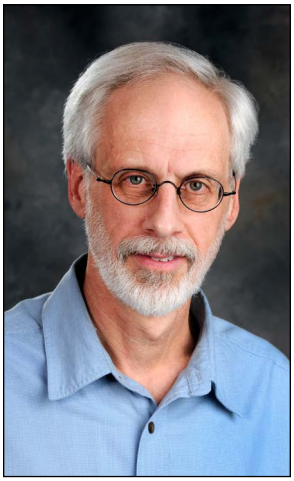

Bucher announced that NTP will conduct additional research to more clearly understand the potential for long-term health effects of the Elk River spill. (Photo courtesy of Steve McCaw)

John Bucher, Ph.D., associate director of the National Toxicology Program (NTP), met July 23 with colleagues from the Centers for Disease Control and Prevention (CDC), a member of Congress, and West Virginia state and local health officials, to discuss plans for conducting additional studies related to a chemical spill earlier this year into West Virginia's Elk River.

Bucher outlined a series of short-term toxicity studies that NTP would conduct on 4-methylcyclohexanemethanol (MCHM) and other chemicals known to be involved in the spill.

In January, approximately 10,000 gallons of chemicals used to process coal spilled from a storage tank into the Elk River. The river is a municipal water source that serves about 300,000 people in the Charleston area.

Based on the limited toxicology information available at the time, scientists judged an MCHM level of one part per million unlikely to be associated with any long-term adverse health effects, and recommended that as the screening level. More details are available on the CDC website.

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Upcoming Events

December 9-10, 2014

NTP Board of Scientific Counselors Meeting

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

May 11-12, 2015

Expert Panel: Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid

Natcher Conference Center
National Institutes of Health
Building 45
10 Center Drive
Bethesda, MD 20894

http://ntp.niehs.nih.gov/about/org/ntpexpertpanel/index.html

June 16-17, 2015

NTP Board of Scientific Counselors Meeting

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

September 2-3, 2015

Scientific Advisory Committee on Alternative Toxicological Methods Meeting

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

All meetings are held at NIEHS unless otherwise noted:

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

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

Federal agencies have continued working to learn more about the chemicals. Since the early days of the incident, NTP has conducted computer modeling to predict potential adverse effects from the chemicals.

This summer, NTP received a request from the CDC Agency for Toxic Substances and Disease Registry to conduct additional toxicity studies.

NTP has published a fact sheet discussing the proposed efforts. Results from the NTP studies should be available within a year.

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

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Peer reviewers support NTP listing recommendation for TCE

By Robin Mackar, reprinted from Environmental Factor, September 2014

A panel of experts spent Aug. 12 peer reviewing an NTP draft monograph on trichloroethylene (TCE), a chemical once prominently used as a degreaser for metal parts. The ten-member panel agreed with the NTP's preliminary decision to list TCE as a known human carcinogen in the Report on Carcinogens (RoC), based on sufficient evidence of carcinogenicity from studies in humans.

The vote came after presentations and discussions by NTP and the reviewers focusing on evidence for cancer at three sites — kidney, liver, and non-Hodgkin lymphoma. An NTP-sponsored public webinar earlier in the year also helped provide information about TCE that was used in the evaluation of the human cancer studies.

An overview of the 30 major human studies used in the TCE evaluation was presented by Jennifer Ratcliffe, Ph.D., of Integrated Laboratory Systems (ILS), a contractor supporting NTP. Ratcliffe went over the study selection and quality evaluation. Stanley Atwood, Ph.D., also of ILS, presented information about the metabolism and genetic effects of TCE.

At the head table, from right, are Director RoC Lunn, Dr.P.H.; panel chair David Eastmond, Ph.D.; Mary Wolfe, Ph.D., NTP deputy division director for policy; and NIEHS and NTP Director Linda Birnbaum. Ph.D. (Photo courtesy of Steve McCaw)

In the audience was Edward Murray, Ph.D., acting director of the Division of Toxicology and Human Health Sciences at the Centers for Disease Control and Prevention Agency for Toxic Substances and Disease Registry. (Photo courtesy of Steve McCaw)

Kidney cancer

Ruth Lunn, Dr.P.H., director of the Office of the Report on Carcinogens, talked the panel through the human studies used by NTP when evaluating kidney cancer outcomes and TCE. She said the studies provide credible evidence of a causal association between increased cancer risk and exposure to TCE.

"The findings are consistent across the studies," Lunn said. "The highest risk for kidney cancer was found in studies where workers were exposed to higher levels of TCE."

Overall, the lead reviewers for the kidney cancer section of the draft had favorable comments. David Richardson, Ph.D., an epidemiologist from the University of North Carolina at Chapel Hill, and others called for more descriptive language to better characterize kidney and other cancers.

The mechanistic studies for kidney cancer were also presented. Reviewer George Douglas, Ph.D., George Douglas Consulting, did not feel there was strong evidence to show a clear mechanism of action of mutagenicity. "I'd call the evidence presumptive and supporting, but not strong."

John Bucher, Ph.D., NTP associate director, reminded reviewers that epidemiological studies alone are enough to provide sufficient evidence of human carcinogenicity. He said identification of a mechanism is not required.

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Non-Hodgkin lymphoma (NHL)

Ratcliffe presented human epidemiological studies on NHL, which is cancer that affects the body's white blood cells. The mechanistic studies were also presented. The panel agreed with NTP's assessment that there is limited evidence of a causal association between exposure to TCE and NHL from studies in humans.

Panel member Sarah Blossom, Ph.D., of Arkansas Children's Hospital Research Institute, commented on the studies focusing on immune effects of TCE that may be related to a mode of action for NHL. "We know it's immunotoxic, but we can't be sure it causes immune suppression."

The panel agreed with the preliminary evidence presented showing limited indication for a causal relationship between exposure to TCE and NHL from studies in humans.

Liver cancer

The human cancer and mechanistic studies were presented by Sanford Garner, Ph.D., also of ILS. Garner started out by saying that liver cancer is a relatively rare cancer and has a low survival rate.

"The data out there are basically inadequate to evaluate the relationship between liver cancer and exposure to TCE," Garner said. He pointed out that TCE-induced liver cancer is likely caused by complex mechanisms involving multiple pathways, including oxidative stress, genotoxicity, and more.

The panel agreed with NTP's preliminary conclusion that there is inadequate evidence of a causal relationship between exposure to TCE and liver cancer.

Overall listing recommendation and next steps

To wrap up the day, chair David Eastmond, Ph.D., of the University of California, Riverside, held a final vote on the preliminary listing decision for TCE.

The panel agreed with NTP that TCE is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans. They went on to say that there are human epidemiological studies showing sufficient evidence for kidney cancer, as well as supporting evidence from toxicokinetic, toxicological, and mechanistic studies. They also agreed that there is limited evidence for TCE from studies of NHL in humans. Supporting evidence for the listing of TCE as a known human carcinogen is also found in animal studies.

NTP will carefully consider all comments made by the panel and the public when revising the draft TCE monograph.

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

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NTP symposium examines indoor air pollution from biomass fuels

By Audrey Pinto and Eddy Ball, reprinted from Environmental Factor, September 2014

An interdisciplinary team of speakers surveyed the state of the science, policy, and future directions of research on adverse health effects of indoor solid fuel combustion, during a symposium Aug. 18 at the National Institute of Environmental Health Sciences (NIEHS), moderated by National Toxicology Program (NTP) toxicologist Cynthia Rider, Ph.D.

Organized and hosted by NTP, the meeting attracted NIEHS grantees and scientists from the U.S. Environmental Protection Agency (EPA) and RTI International, as well as researchers funded by nonprofits and other agencies. Attendees are dedicated to improving the health of the estimated 3 billion people worldwide who burn biomass such as wood, dried dung, peat, and other organic solids in indoor cookstoves and fire pits to cook their traditional food and heat their homes (see fact sheet).

Rider is project leader on the NTP PAC mixtures assessment study. Along with moderating the meeting and introducing speakers, she also reported on her group's research. (Photo courtesy of Steve McCaw)

As NIEHS and NTP Director Linda Birnbaum, Ph.D., said in her welcome and introduction, some 4 million people die prematurely each year from cancer and other diseases directly caused or worsened by exposure to indoor air pollution from biomass combustion. She described a complex exposure, involving mixtures that are not completely understood, and improved cookstove interventions that are not always effective or adopted by the people who need them.

According to Birnbaum, the problem directly relates to priority themes and goals of the NIEHS strategic plan and crosses several disciplines with implications for human rights, gender inequities, community engagement, and health disparities. "I think it's especially an issue for women and children," she said.

"Some of the [indoor] exposures make Beijing look clean," Birnbaum said as she described the conditions in homes using firepits and makeshift stoves. (Photo courtesy of Steve McCaw)

A real commitment, but much more is needed

Birnbaum was followed by Claudia Thompson, Ph.D., who described the impressive NIEHS grants portfolio on cookstoves and the NIEHS-World Health Organization (WHO) Collaborating Centre for Environmental Health Sciences emphasis on translation and capacity building in developing countries.

Elaborating on themes introduced by Birnbaum and Thompson, keynote speaker Sumi Mehta, Ph.D., director of programs for the 1,000-partner Global Alliance for Clean Cookstoves (GACC), described the group's goal of supplying 100 million households with improved cookstoves by 2020 through what she called an integrated market approach.

Mehta pointed to some of the gaps in knowledge and performance that must be addressed, including the discrepancy between lab performance and field performance of new technology, as well as the importance of demonstrating that adoption of improved cookstoves can actually save lives. There remain important co-exposures, such as kerosene lighting and second-hand smoke, that need to be better understood.

Analyzing exposures

Work on better understanding exposures is well underway at EPA and NTP. David DeMarini, Ph.D., a genetic toxicologist with EPA, addressed "Mutagenicity Emission Factors of Cookstoves: Health Effects Implications Relative to Other Combustion Emissions," as part of the morning session's four EPA cookstove research presentations.

Regarding test data from natural draft (ND) and forced draft (FD) cookstoves with analysis of fine particulate matter (PM 2.5) for 32 polycyclic aromatic hydrocarbons, DeMarini said, "It does reinforce how bad all of the stoves are compared to propane." He found that even FD, the safest and most efficient of the biomass stoves, is far from safe. "FD has a mutagen factor based on fuel energy similar to that of diesel, a known carcinogen," he said.

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"Even the best stoves are not safe without adequate ventilation," DeMarini cautioned. He said the ND, or rocket stove, is no better than the three-stone fire pit in use in many households, noting that vastly less pollution is produced by liquid and gas stoves, which perform as much as 100 times better than stoves burning solid fuels.

In her afternoon talk, Rider explained that the NTP polycyclic aromatic compound (PAC) mixtures assessment program is contributing data toward developing a methodology for risk assessment of whole mixtures of PACs. "We want to assess emission samples from cookstoves and woodstoves collected by field researchers," she said. "This unique approach creates an unprecedented opportunity for multidisciplinary cooperation to better understand and inform communities of potential health risks of PAC exposure."

Lessons from the field

Tony Ward, Ph.D., an environmental health scientist at the University of Montana, discussed a successful outreach project in Libby, Montana. "[People] were breathing in high levels of particulate matter outdoors and inside their homes during the winter months," explained Ward. A unique community-based partnership provided Libby residents with EPA-certified wood-burning stoves, significantly reducing pollution levels.

Marc Jeuland, Ph.D., an environmental economist at Duke University, and Pam Jagger, Ph.D., an applied political economist at The University of North Carolina at Chapel Hill, working in India and Malawi, respectively, explained the challenges of getting rural villagers to adopt improved cookstoves (see text box). Both researchers suggested that continuous community involvement and marketing campaigns might boost improved cookstove use.

Next generation of researchers

The final speakers, Eleanne van Vliet, a Dr.P.H. student at Columbia University, and Lucia Pruneda-Alvarez, a Ph.D. student at the Universidad Autonoma de San Luis Potosi, shared preliminary findings on the health effects of biomass fuels and PACs among Ghanian and Mexican women and children.

In concluding the meeting, a common theme emerged — there are tremendous challenges ahead that will require multidisciplinary, innovative approaches to improve the health of affected populations.

(Audrey Pinto, Ph.D., is technical editor for the journal Environmental Health Perspectives.)

Challenges and barriers

The complexity of human nature is never more apparent than when public health attention turns to behavior change, particularly age-old behaviors centered around food and cooking.

In the afternoon sessions, the scientists discussed some of the barriers to successful adoption of improved technologies among many low-income and rural communities.

- Perception — people in rural communities are not aware of the health benefits of reducing indoor and outdoor air pollution. As Jagger observed, "The doctors in Malawi have no idea that air pollution is a major cause of disease in their country."
- Infrastructure — supply and demand depends on whether rural communities have access to stoves and a reliable source of electricity.
- Socioeconomic status — many people in rural communities are very poor, so the cost of improved cookstoves is prohibitive, especially if it involves structural changes to houses to provide effective chimneys.

Take-home messages

Improved cookstove adoption is positively related to perceptions of health and time savings.

Peer pressure and social norms as perceived through the actions of neighbors may be important.

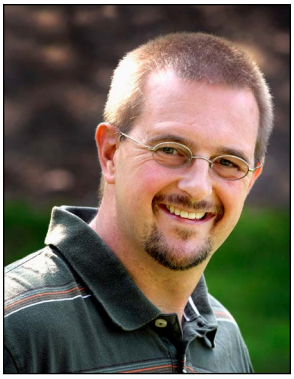
Continuous involvement of heads of households must be maintained.

A combination of supply-chain improvements and carefully designed social marketing and promotion campaigns, and possibly incentives, to reduce the up-front cost of stoves may increase adoption and use of improved cookstoves in some areas.

As Jeuland concluded, "The key to real results and health benefits is reducing exposures. We must expand our scope to address what the communities want to do. In the end, we may be expecting a lot from a little stove."

A new approach to determine cancer risk of chemicals

By Sara Mishamandani, reprinted from Environmental Factor, September 2014



Auerbach is a member of the NIEHS Molecular Toxicology and Informatics Group within the Biomolecular Screening Branch (BSB). He is responsible for oversight of the NTP DrugMatrix database and ToxFX toxicogenomics analysis tool. (Photo courtesy of Steve McCaw)

A new study by National Institute of Environmental Health Sciences (NIEHS)-funded researchers at Boston University (BU) and the National Toxicology Program (NTP) has shown that computational models of short-term exposure to a chemical can predict long-term cancer risk. The study, led by computational biologist Stefano Monti, Ph.D., an associate professor at BU, is a step toward simpler and cheaper tests to screen chemicals for cancer risk.

The current gold standard for testing chemicals for cancer risk is a two-year rodent bioassay, which can cost $2 million to $4 million per chemical to complete. As a result, less than 2 percent of the approximately 84,000 chemicals in commercial use have gone through standard carcinogenicity testing.

"Not enough attention is given to understanding chemicals before they are used by industry and released into the environment," said Monti. "This work has confirmed that it is possible to predict the long-term cancer risk by measuring the short-term effects."

Understanding response to chemicals in the body

According to the authors, high-throughput genomic approaches have been applied to understand how cancer is initiated and progresses, to identify therapeutic targets, and to discover biological markers of cancer. However, using these methods to study environmental causes of cancer has not received as much attention.

Researchers at BU teamed up with NTP molecular toxicologist Scott Auerbach, Ph.D., to build on current genomic analysis technologies and develop affordable approaches to predict carcinogenicity and toxicity of thousands of environmental chemicals and mixtures. As part of this effort, BU Superfund Research Program (SRP) Center Director David Sherr, Ph.D., and Monti are developing a platform for predicting chemical toxicity and carcinogenicity.

Using a data set from the NTP DrugMatrix database, researchers compared gene expression responses to known carcinogens and noncarcinogens. From the data, they developed a predictive model to discriminate between the two. They also identified differentially expressed genes associated with cancer-causing chemicals and were able to zoom in on the potential mechanisms driving the initiation of cancer.

Moving forward

In the study, the researchers validated the model to predict carcinogenicity, using two large, rat-based gene datasets. They found that carcinogenicity predictions depend on the tissue exposed to the chemical of interest and confirmed and expanded on several previous studies implicating DNA damage, the aryl hydrocarbon receptor, and other pathways in the response to carcinogen exposure.

To their knowledge, the data collection they assembled represents the largest toxicogenomics resource analyzed to date. The collection allows the scientists to continue to evaluate issues related to variability in studies, differences due to tissue, exposure dose and length, sample size, and other factors, to achieve the maximum predictive accuracy using the model.

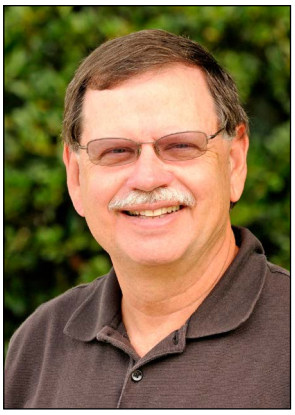
According to the authors, despite an overall decrease in incidence of and mortality from cancer, about 40 percent of Americans will be diagnosed with the disease in their lifetime, and around 20 percent will die of it. By further developing this platform for use, researchers will be able to better predict carcinogenicity and understand the biological process and pathways affected by exposure to different chemicals.

Citation: Gusenleitner D, Auerbach SS, Melia T, Gomez HF, Sherr DH, Monti S. 2014. Genomic models of short-term exposure accurately predict long-term chemical carcinogenicity and identify putative mechanisms of action. PLoS One 9(7):e102579.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

Predictive toxicology advances with new paper and data challenge

By Eddy Ball, reprinted from Environmental Factor, August 2014



Tice was part of the five-member team of lead researchers who designed the study, which tested the 10K library in triplicate for each assay and evaluated the performance of the two assays. (Photo courtesy of Steve McCaw)

Tox21

Tox21 is a collaborative effort among National Institutes of Health (NIH) partners National Toxicology Program (NTP) and National Center for Advancing Translational Sciences (NCATS), the U.S. Environmental Protection Agency, and the U.S. Food and Drug Administration (FDA).

Now in Phase II of the program, the consortium is working to develop a model for rapidly anticipating adverse responses to potentially harmful drugs and chemicals, through *in vitro* screening using multiple assay approaches, and prioritizing chemicals for more comprehensive testing with more resource-intensive test methods.

In July, partners in the Tox21 consortium published a new study on pathway profiling of the Tox21 compound library, and announced a chemical toxicity data model competition.

"We are entering an exciting phase of Tox21," said NIEHS and NTP Director Linda Birnbaum, Ph.D. "According to the latest count from NCATS, the consortium partners have screened the 10,000 compound library against cell-based assays and produced nearly 50 million data points."

"Now the challenge is to develop advanced predictive models for analyzing and understanding this massive amount of data," she said. "This is an important part of our ongoing mission to improve environmental public health and prevent disease, by addressing the backlog of thousands of untested chemicals."

The new study, published July 11 in Nature Publishing Group's Scientific Reports, contains the latest data emerging from screening of the Tox21 library of approximately 10,000 (10K) environmental chemicals and drugs, for agonists and antagonists of the estrogen receptor (ER) alpha signaling pathway. The 22-member team included NTP scientists, led by Biomolecular Screening Branch head Raymond Tice, Ph.D., and scientists from Tox21 consortium partner agencies (see text box).

The Tox21 chemical toxicity data model competition, launched by NCATS, is an effort to crowdsource data analysis by independent researchers, to reveal how well they can predict a compound's interference in biochemical pathways, using only chemical structure data. The compound profiling studies and data model competition are key components of the Tox21 initiative to develop next-generation predictive toxicology using quantitative high-throughput screening (qHTS) of chemicals.

Profiling potential endocrine-disrupting compounds

Using two ER reporter gene cell line assay formats, the Tox21 team screened chemicals for their effects on the ER alpha signaling pathway that may disrupt endocrine function in humans through unwanted interactions of chemicals with steroid hormone receptors.

Estrogenic effects occur through the numerous ER target genes that are either upregulated (agonized) or downregulated (antagonized) in response to ligand-induced activation of ERs. Both responses to estrogen produced by the body, or to such compounds as therapeutic agents, industrial chemicals, pesticides, and plasticizers can have potentially adverse effects on development, reproduction, and metabolic homeostasis, or balance.

According to the researchers, the results of their study support the feasibility of qHTS to identify environmental chemicals with the potential to interact with the ER alpha signaling pathway. Additionally, the two different assay formats improve the confidence in correctly identifying these chemicals.

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Helping the data speak a language we can understand

"The Tox21 program is a wonderful example of what can be accomplished when government agencies join forces and pool resources," said NCATS Director Christopher Austin, M.D., in the announcement of the competition.

"Our researchers have generated more data about chemical toxicity than we can realistically analyze and understand without additional collaboration," he explained. "Similar to many other large-scale scientific endeavors that generate public data, we have created the 2014 Tox21 data challenge to crowdsource the best predictive models from researchers across the globe."

The computational model submission deadline is Nov. 14. NCATS will announce the winners in January 2015.

Citation: Huang R, Sakamuru S, Martin MT, Reif DM, Judson RS, Houck KA, Casey W, Hsieh JH, Shockley KR, Ceger P, Fostel J, Witt KL, Tong W, Rotroff DM, Zhao T, Shinn P, Simeonov A, Dix DJ, Austin CP, Kavlock RJ, Tice RR, Xia M. 2014. Profiling of the Tox21 10K compound library for agonists and antagonists of the estrogen receptor alpha signaling pathway. Sci Rep 4:5664.

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ICCVAM engages interest groups at public meeting

By Catherine Sprankle, reprinted from Environmental Factor, August 2014

Members of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) met with representatives of industry, academia, and animal welfare organizations, to discuss alternatives for chemical and product safety testing.

The June 25 public forum was held at the National Institutes of Health in Bethesda, Maryland.

Updates from member agencies

ICCVAM co-chair Anna Lowit, Ph.D., from the U.S. Environmental Protection Agency (EPA), summarized ICCVAM activities since the September 2013 meeting of the Scientific Advisory Committee on Alternative Toxicological Methods. She also provided updates on ICCVAM scientific focus areas, plans for improved stakeholder communication, and new paradigms for test method validation.

Joanna Matheson, Ph.D., of the U.S. Consumer Product Safety Commission, detailed activities in one of ICCVAM's priority areas — skin sensitization. "Because the adverse outcome pathway for skin sensitization is well-characterized, and a number of nonanimal test methods have been developed, it has great promise for the near-term development of testing strategies that do not require the use of animals," she noted. To reach this goal, ICCVAM is actively collaborating with its European counterparts and industry to identify an optimal strategy.

Agencies highlight ongoing activities

After a summary of National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) activities by Director Warren Casey, Ph.D., other ICCVAM member agencies highlighted their activities relevant to replacing, reducing, or refining animal use.

Lowit, her fellow co-chair Abigail Jacobs, Ph.D., of the U.S. Food and Drug Administration (FDA); and ICCVAM members Raymond Tice, Ph.D., from the National Institute of Environmental Health Sciences (NIEHS); Barnett Rattner, Ph.D., from the U.S. Department of the Interior (DOI); and Christine Kelley, Ph.D., of the

Casey discusses nonanimal testing approaches with regulators

A key point raised by public forum participants — training regulatory agency reviewers on the applicability and availability of nonanimal test methods and strategies — was precisely the topic Casey discussed with EPA personnel in a June 24 webinar titled "Validation and Utilization of Alternative Test Methods."

Casey presented an overview of internationally accepted nonanimal methods for identifying substances that can cause skin or eye irritation. He discussed current efforts to develop strategies that use data from multiple sources to arrive at a hazard classification for potential skin sensitizers — an approach that may soon enable elimination of animal testing for this purpose.

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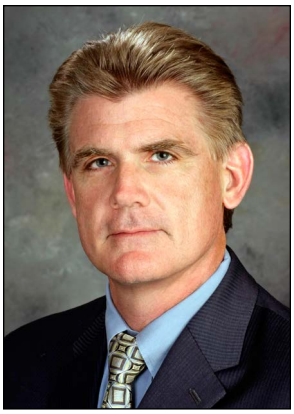

In his presentation at the forum, Casey highlighted NICEATM's ongoing projects, including efforts associated with endocrine disruptor screening methods, aquatic models of toxicity testing, extrapolation of *in vitro* data to *in vivo* effects, and adverse outcome pathways. (Photo courtesy of Steve McCaw)

National Institutes of Health (NIH), gave updates on a wide spectrum of activities. These ranged from near-term solutions, such as product-specific validation of nonanimal methods, to longer-term, more complex approaches, such as organs-on-a-chip, to predict human health hazards and minimize animal use.

Key points raised in response to the agency updates and during the open comment period included requests for increased transparency in reporting animal use by industry, and the need for adequate training on nonanimal test methods for reviewers at ICCVAM regulatory agencies (see side bar on page 9).

Casey closed the meeting by noting that ICCVAM plans to hold similar events annually. "We want to ensure that our stakeholders have ample opportunity to interact in person with ICCVAM, by having these types of open dialogue," he said, encouraging all participants to provide feedback on how the meetings could be improved.

NICEATM, which supports ICCVAM, organized the forum.

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

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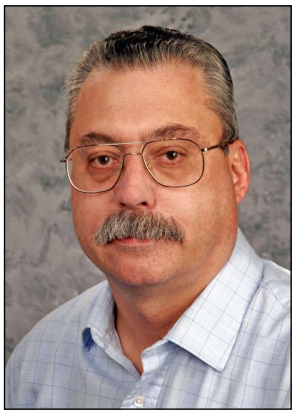
NIEHS researchers show low doses of arsenic cause cancer in male mice

By Robin Mackar, reprinted from Environmental Factor, August 2014

Michael Waalkes, Ph.D., knows how to end his career on a high note. Waalkes was head of the National Toxicology Program (NTP) Laboratory until his retirement in June, after 31 years of federal service. He and his colleagues in NTP published a paper July 9 in the journal Archives of Toxicology with far-reaching impact, showing that mice exposed to low doses of inorganic arsenic in drinking water, similar to what some people might consume, developed lung cancer.



The study is a paradigm shift for low dose studies, said Waalkes, who is known for his research capabilities and mentoring of future scientists. (Photo courtesy of Steve McCaw)

Erik Tokar, Ph.D., biologist in the NTP Inorganic Toxicology Group and a co-author on the paper, presented the new findings to Her Royal Highness Princess Chulabhorn of Thailand, founder and president of the Chulabhorn Research Institute, during her visit July 11 to NIEHS (see story). (Photo courtesy of Steve McCaw)

Whole life model duplicates human exposure

The Waalkes team used a model that mimics how humans are exposed to arsenic over their lifetime. Mice were given arsenic in their drinking water three weeks before breeding, as well as throughout pregnancy and lactation. Arsenic was then given to the offspring after weaning, and all through adulthood, at concentrations relevant to human exposure. The researchers then examined tumors in the adult offspring.

Concentrations in the drinking water were 50 parts per billion (ppb), 500 ppb, and 5,000 ppb. The 50 ppb dose is the lowest concentration tested in an animal study, and many researchers feel that differing rates of metabolism and excretion mean that mice need to be exposed to greater concentrations than humans to achieve similar internal doses.

"This is the first study to show tumor development in animals exposed to very low levels of arsenic — levels similar to which humans might be exposed," said Waalkes. "The results are unexpected and certainly give cause for concern."

Arsenic is present in the environment, both as a naturally occurring substance and due to contamination from human activity. Arsenic may be found in many foods, including grains, fruits, and vegetables, due to plant absorption from soil

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and water. This study focused on inorganic arsenic, which occurs in the drinking water of millions of people worldwide and is known to be a human carcinogen that targets the lung and several other sites. More information about arsenic can be found in a newly developed National Institute of Environmental Health Sciences (NIEHS) fact sheet.

Findings add to growing evidence of low dose effects

More than half of the male offspring in the study developed significant increases in benign and malignant lung tumors at the two lower doses (50 ppb and 500 ppb). Female offspring also developed benign tumors at the lower concentrations. Interestingly, the researchers did not find significant increases in lung tumors in either sex at the highest dose (5,000 ppb).

"Although this is only one study, it adds to a growing body of evidence showing adverse health effects from very low exposures to arsenic, raising the possibility that no level of arsenic appears to be safe," said Linda Birnbaum, Ph.D., NIEHS and NTP director.

Citation: Waalkes MP, Qu W, Tokar EJ, Kissling GE, Dixon D. 2014, Lung tumors in mice induced by "whole-life" inorganic arsenic exposure at human-relevant doses. Arch Toxicol 88(8):1619-1629.

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

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Advisory committee gives thumbs up to progress on alternative methods

By Ernie Hood, reprinted from Environmental Factor, October 2014

"These collaborations are exactly the type of activity that was envisioned when the ICCVAM Authorization Act was passed 15 years ago, and they will ultimately bring success in implementing methods to reduce, refine, and replace animals in toxicity testing," said Birnbaum. (Photo courtesy of Steve McCaw)

Finding alternatives to animal testing

The term alternative methods refers to methods of research and testing that use fewer or no animals, or that reduce animal pain and distress. The National Toxicology Program (NTP) participates in three committees that ensure the involvement of all stakeholders in the advancement of alternative testing methods.

- The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) coordinates the activities of member federal agencies to replace, reduce, or refine animal use.
- The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) supports ICCVAM activities and NTP high-throughput screening projects. The center conducts projects relevant to test method development, maintaining and promoting scientific quality and the protection of human and animal health and the environment.
- The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) advises NICEATM, ICCVAM, and the NIEHS and NTP director. Representatives are drawn from industries regulated by ICCVAM member agencies, animal welfare organizations, academia, test method developers, and regulatory agencies outside of the federal government.

The Scientific Advisory Committee on Alternative Toxicological Methods gave an enthusiastic thumbs-up to the substantial reinvention launched last year by the groups it advises. The advisory committee met Sept. 16 at NIEHS to review work of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), and the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Methods (see text box).

"It's been just over a year since ICCVAM released its new vision and strategic direction, which outlined a new plan and a new direction for the 15-member U.S. committee," said Linda Birnbaum, Ph.D., NIEHS and NTP director. "You're going to hear about some of the significant progress that has been made by the committee on a variety of fronts since the plan was adopted."

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Fit-for-purpose approach

Perhaps most importantly, the coordinating committee has adopted an approach to validation of alternative test methods known as a fit-for-purpose approach. The method focuses on the needs of individual agencies and industries that are best positioned to quickly adopt a specific alternative test method.

Warren Casey, Ph.D., director of the interagency center, explained that the coordinating committee has evolved into more of a service organization. "Fit-for-purpose validation is really getting the right product to the right person at the right time, or getting the agencies what they need when they need it — high-quality results in a very short amount of time," he said.

Words have become deeds

Last year's good intentions formed the basis of this year's tangible accomplishments, making for action-oriented updates from the coordinating committee, the federal agencies that comprise the coordinating committee, the interagency center, and international alternative methods agencies, such as those in the European Union, Japan, Canada, and Korea. Several speakers noted that collaborations among agencies and other stakeholders have increased dramatically and substantial progress has been made toward acceptance of alternative methods.

As a key element of new vision and direction, the coordinating committee and interagency center increased engagement with the scientific community and stakeholders through focused workshops (see related story), webinars, and forums. Website upgrades have helped improve communication with stakeholders.

"We are very pleased with ICCVAM's new direction and its much stronger focus on achieving real reductions in animal use," said Patricia Bishop, People for the Ethical Treatment of Animals representative, echoing the positive sentiments expressed by many of the advisory committee members. ●

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

A mild, late summer day was the perfect opportunity to collect the committee members and attendees outdoors for a group photo. (Photo courtesy of Steve McCaw)

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World Congress strengthens international ties

By Catherine Sprankle

NICEATM and ICCVAM strengthened international ties Aug. 24-28 at the Ninth World Congress on Alternatives and Animal Use in the Life Sciences in Prague.

- NICEATM staff helped organize a satellite meeting, "Workshop on Alternatives to the HIST for Acellular Pertussis Vaccines: Progress and Challenges in the Replacement of HIST."
- Casey co-chaired the Activity Updates From International Validation Centers session and summarized NICEATM and ICCVAM activities.
- NICEATM contractor Nicole Kleinstreuer, Ph.D., gave two presentations — one on an adverse outcome pathway for vascular development toxicity, and another on using high-throughput screening methods to identify endocrine disruptors.
- Raymond Tice, Ph.D., of NTP, co-chaired two sessions — Updates on Research Activities from the USA, and High-throughput Screening Models. He also presented updates on Tox21 activities.
- Abigail Jacobs, Ph.D., ICCVAM co-chair, with FDA, co-chaired the Topical Toxicity-Phototox session. She also gave a presentation on internationally harmonized nonanimal approaches to photosafety testing.
- Suzanne Fitzpatrick, Ph.D., with FDA, co-chaired and gave a presentation at the Tissues and Organs-on-a-Chip session. She also presented the regulatory perspective on adverse outcome pathways, and a process for international cooperation on regulatory science.
- Richard McFarland, Ph.D., with FDA, discussed reducing, refining, and replacing animal use in preclinical testing of cellular and gene therapies.
- Staff from NICEATM and the NTP Biomolecular Screening Branch prepared and presented eleven scientific posters.

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Adverse outcome pathway workshop generates enthusiasm and collaboration

By Catherine Sprankle, reprinted from Environmental Factor, October 2014

At the opening session, Austin related the adverse outcome pathways concept to research translation, which is the process of turning laboratory observations into interventions that improve the health of individuals and the public. (Photo courtesy of Catherine Sprankle)

A workshop Sept. 3-5 at the National Institutes of Health (NIH) in Bethesda, Maryland, brought together scientists from 21 countries, representing industry, academia, regulatory agencies, and special interest groups. The workshop, Adverse Outcome Pathways: From Research to Regulation, considered how the adverse outcome pathway concept could improve regulatory assessments of chemical toxicity. The National Toxicology Program Interagency Center for the Evaluation of Alternative Methods (NICEATM) co-sponsored the workshop with the nonprofit Physicians Committee for Responsible Medicine.

An adverse outcome pathway organizes existing knowledge on chemical mode of action, for example, from an initiating event such as receptor binding, through key processes, and ending with an adverse outcome such as disease or toxicity.

The workshop featured plenary presentations, as well as breakout sessions to consider adverse outcome pathway applications, development of new pathways, and challenges to their adoption. Participants appreciated the collaborations and enthusiasm that the workshop generated, and the closing session emphasized the need to maintain that momentum.

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Better understanding and practical applications

In his opening remarks, Christopher Austin, M.D., head of the NIH National Center for Advancing Translational Sciences, characterized the process of predicting toxicity as a grand challenge. "Traditionally we have exposed animals or humans and waited for the outcome at the other end, without understanding what goes on in between," he said. "This limits our understanding of mechanisms by which these things happen."

In addition to supporting a better understanding of how disease develops after chemical exposure, adverse outcome pathways help identify where more research is needed to understand underlying mechanisms, aid in chemical classification and prioritization for future testing, and guide the development of new testing approaches that use fewer or no animals.

Two well-received presentations demonstrated online tools for developing and sharing pathways. Stephen Edwards, Ph.D., of the U.S. Environmental Protection Agency, previewed a new wiki launched in September by the Organisation for Economic Co-operation and Development. Hristo Aladjov, Ph.D., a consultant at the Organisation, demonstrated Effectopedia, an online data collection and collaboration tool for delineating pathways. "I really appreciated the Effectopedia demonstration," commented one attendee. "I want to download it as soon as I get home!"

Participants look forward

"I don't think I've ever seen this much energy associated with a workshop," noted Warren Casey, director of NICEATM, which committed to establishing and managing an email list to keep attendees informed of related activities.

Presentations and links to webcasts from the workshop will be posted, and a workshop report will be published early next year.

Resources for development of adverse outcome pathways

An adverse outcome pathway (AOP) is an approach to organizing existing knowledge on chemical mode of action, starting with an initiating event such as receptor binding, continuing through key events, and ending with an adverse outcome such as disease or toxicity. NICEATM is working with U.S. and international collaborators to develop AOPs for several toxicity areas. The following resources supporting development of adverse outcome pathways are now available.

- The Organisation for Economic Co-operation and Development (OECD) has launched the AOP Wiki, a resource for developing and sharing AOPs. This Wiki is the first module of the OECD Adverse Outcome Pathways Knowledge Base, which will provide a focal point for AOP development and dissemination. Information about the AOP Wiki and a User Handbook is available on the OECD website at http://www.oecd.org/chemicalsafety/launch-adverse-outcome-pathways-knowledge-base.htm.
- NICEATM and the Physicians Committee for Responsible Medicine held a workshop on "Adverse Outcome Pathways: From Research to Regulation" on September 3-5. Materials from the workshop, including links to the plenary session videocasts and summaries of the breakout group discussions, are available on the NTP website.
- Also on the NTP website is a link to the Adverse Outcome Pathways Community listserv, an email list managed by NICEATM to provide information about events and activities of interest to AOP developers and users. You may also subscribe to the list on the NIH website.

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

By Catherine Sprankle

ICCVAM releases 2012-2013 Biennial Report

The latest Biennial Report of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was released on July 29. The report describes ICCVAM and ICCVAM agency activities during the period from January 2012 through December 2013. It highlights ICCVAM member agency research activities supporting toxicology innovation in eye safety testing, biologics and vaccine testing, development of tests to identify potential skin sensitizers, and other areas. The report also summarizes regulatory agency initiatives to promote replacement, reduction, and refinement of animal use and provide information about use of *in vitro* methods.

ICCVAM is a committee of representatives of 15 federal agencies that generate or use toxicological testing data. Supported by NICEATM, ICCVAM promotes the use and acceptance of new test methods that better protect health and replace, reduce, or refine animal use.

The 2012-2013 ICCVAM Biennial Report is available on the NTP website.

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In memory of Cheryl Scott

By Ruth Lunn

Cheryl Siegel Scott, M.S.P.H., head of the U.S. Environmental Protection Agency (EPA) Quantitative Risk Methods Group, National Center for Environmental Assessment, and National Toxicology Program (NTP) technical advisor, died peacefully at her home in Arlington, Virginia, on Aug. 24, 2014.

Cheryl was a well-respected epidemiologist and valued member of the EPA for over 33 years. Her leadership and expertise in many facets of risk assessment made her an important contributor to scientific reviews on environmental chemicals' health effects. In recent years, Cheryl played a key role in EPA's scientific assessments for trichloroethylene (TCE). In 1999, Cheryl was the guest editor of a special issue in Environmental Health Perspectives on the state of the science for multiple publications associated with the development of the EPA TCE assessment, and co-authored several scientific publications on health effects of TCE since that time.

We would like to especially recognize her recent contributions to the NTP. Cheryl served as a technical advisor for the NTP review of TCE for possible change in listing status in the Report on Carcinogens. She provided advice to NTP for conducting the evaluation, served as a moderator for the March 14, 2014, public webinar on "Human Cancer Studies on Exposure to Trichloroethylene (TCE): Methods Used to Assess Exposure and Cancer Outcomes," and provided critical and helpful comments on the human cancer section of the draft Report on Carcinogens monograph on TCE. The draft monograph was peer-reviewed by a panel of experts on Aug. 12, 2014.

Cheryl brought intelligence, skill, organization, and diligence to her contributions to risk assessment and particularly the use of epidemiology data. Her spirit, energy, and fairness to all were strong traits that others could see and welcomed.

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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

NTP Study Reports and Publications Available at: http://ntp.niehs.nih.gov/go/reports

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