UPDATE
National Toxicology Program

JANUARY 2010

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

What's Inside:

NTP Outlines Challenges and Directions at Meeting of Scientific Counselors

Article by Thad Schug, reprinted from *eFACTOR*, January 2010

The National Toxicology Program (NTP) is "working to do more in terms of developing toxicology testing across the Federal government," declared NIEHS/NTP Director Linda Birnbaum, Ph.D., as she opened a two-day meeting before the NTP Board of Scientific Counselors (BSC) at NIEHS December 9-10. Birnbaum's themes of NTP leadership and innovation in toxicity testing in the 21st century through expanded partnerships with other agencies emerged repeatedly in the packed agenda.

In the course of the day and a half meeting, the Board heard presentations on activities by the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR), concepts for contracts, a review of the Host Susceptibility Program, research concepts for NTP testing nominations, and an overview of NTP studies on herbals and supplements.

Bucher points to interagency collaborations on toxicity testing

NTP Associate Director John Bucher, Ph.D., followed Birnbaum with an update on recent programmatic activity and staff changes within the NTP. He also announced the opening of a shared NTP laboratory to be used by scientists to "better address the toxicological effects occurring in developmental periods that may result in long-term chronic disease later in life."

Nomination proposes state-of-science literature review on obesity/diabetes

Early in the meeting Kristina Thayer, Ph.D., acting director of CERHR, presented a concept nomination to explore the "state-of-the-science evaluation of environmental exposures and diabetes and obesity." Thayer said that the association between environmental contaminates and diabetes and obesity is an emerging topic of health concern in need of a focused review.

Thayer proposed that CERHR convene a panel of external scientists and hold a workshop to evaluate emerging literature for consistency and relevance and to provide direction for future research. Thayer's presentation sparked a lively debate among Board members on the difficulties of identifying impact issues in an area of health science undergoing such rapid development.

Board reviews projects on host susceptibility

John (Jef) French, Ph.D., acting chief of the NTP Host Susceptibility Branch (HSB), spent a large part of the afternoon session updating the Board on the state of 8 projects in various stages of development within the HSB. French highlighted examples of several genetic variability testing projects with mice strains that the HSB considers "critical to understanding the role of population genetics in the origin and progression of environmental exposure related to toxicity and disease."

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Nominations highlight tiered testing protocol

Scott Masten, Ph.D., director of the NTP Office of Nomination and Selection, kicked off day two of the meeting with the nomination of five chemicals for Board consideration for extensive NTP testing. NTP Project leaders and Board members reinforced another position expressed earlier by Bucher and Birnbaum — that the NTP should "work to establish a better understanding of risk assessments associated with dosimetry, particularly during critical developmental periods."

The Board and members of the public, including People for the Ethical Treatment of Animals representative Joseph Manuppello, commented on the importance of conducting *in vitro* studies prior to animal testing. NTP scientists addressed these concerns by outlining a tiered testing strategy in which NTP first tests chemical toxicity in cell-based assays before moving to animal models.

Dietary supplements become a higher priority for toxicity testing

As part of the program's emphasis on determining toxicity of dietary supplements, three of the five chemicals nominated for future NTP testing were the herbal medicines butterbur, evening primrose oil, and valerian. NTP Deputy Program Director for Science Nigel Walker. Ph.D., wrapped up the meeting with a presentation on the NTP Dietary Supplements and Herbal Medicines Initiative, placing new and existing nominations into a context of interagency public health collaboration.

Walker noted that dietary supplements are a multi-billion dollar industry of products that often lack uniform strength, purity, and composition — presenting special challenges for toxicity testing. Walker stated that dietary supplement testing will remain a major priority for NTP, which is leading efforts to "increase coordination across federal agencies to ensure NTP obtains the most needed information to inform public health decision making." ●

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

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Collegium Ramazzini Elects Birnbaum as Fellow

Article by Eddy Ball, reprinted from *eFACTOR*, January 2010

NIEHS/NTP Director Linda Birnbaum, Ph.D., received notification in December of her election as a fellow of the Collegium Ramazzini headquartered in Carpi, Italy. The letter from Collegium Ramazzini Secretary General Morando Soffritti, M.D., praised Birnbaum for her "scientific stature and authority" and "commitment to the public's health."

Birnbaum described her election as "a great honor" and said she looks forward to working with this prestigious group.

Birnbaum recognized for international distinction in environmental health

With 180 fellows in 30 countries, the Collegium Ramazzini is an international scientific society that examines critical issues in occupational

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Upcoming Events

May 10, 2010

NTP Board of Scientific Counselors

NIEHS, 111 TW Alexander Dr.
Research Triangle Park, NC

June 17-18, 2010

Scientific Advisory Committee on Alternative Toxicological Methods

U.S. Environmental Protection Agency
109 TW Alexander Dr.
Research Triangle Park, NC

June 21-22, 2010

NTP Board of Scientific Counselors

NIEHS, 111 TW Alexander Dr.
Research Triangle Park, NC

September 14-16, 2010

International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing

Sponsor: NICEATM-ICCVAM
NIH Natcher Conference Center
Bethesda, MD

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

and environmental health, with a view towards action to prevent disease and promote health. The fellows are professionals of clear personal distinction and integrity, distinguished by their contributions to occupational and environmental health.

Birnbaum is one of the select group of current and former NIEHS scientists who are Collegium Ramazzini fellows. They include former NIEHS Director Ken Olden, Ph.D., NTP Associate Director John Bucher, Ph.D., and Superfund Research Program Director William Suk, Ph.D., as well as current and former NIEHS scientists Carl Barrett, Ph.D., James Huff, Ph.D., George Lucier, Ph.D., Ronald Melnick, Ph.D., and Walter Rogan, Ph.D. Former NIEHS Director David Rall, M.D., Ph.D., was both a fellow and the recipient of the annual Ramazzini Award in 1989.

The Collegium Ramazzini carries on the legacy of the father of occupational medicine

Founded in 1982, the Collegium derives its name from Italian physician and University of Modena Professor Bernardino Ramazzini (1633–1714), who authored one of the founding and seminal works of occupational medicine and played a substantial role in its development. His book, De Morbis Artificum Diatriba (Diseases of Workers), outlined the health hazards of chemicals, dust, metals, repetitive or violent motions, odd postures, and other disease-causative agents encountered by workers in 52 occupations.

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NIEHS Awards Recovery Act Funds to Address Bisphenol A Research Gaps

Researchers studying the health effects of the chemical bisphenol A (BPA) gathered in North Carolina to launch an integrated research initiative to produce data that will allow for a comprehensive assessment of its possible human health effects.

Researchers who just received funds from the American Recovery and Reinvestment Act to study BPA were brought together to meet with scientists from academia and government already working on the compound. The meeting was held Oct. 6, 2009 at the National Institute of Environmental Health Sciences (NIEHS).

The meeting is part of an effort to support human and animal research that will help determine if current exposures to BPA in the general population pose a potential health risk. NIEHS is part of the National Institutes of Health (NIH) and has the lead in supporting research to study the potential effects that chemicals, such as BPA, may have on human health. President Obama allocated $5 billion in Recovery Act funds to the NIH, with about $14 million going to NIEHS for research on BPA.

“We know that many people are concerned about bisphenol A and we want to support the best science we can to provide the answers,” said Linda Birnbaum, Ph.D., who serves as director of the NIEHS and the National Toxicology Program (NTP), an interagency program for the U.S. Department of Health and Human Services. “Bringing the key BPA researchers together at the onset of new funding will maximize the impact of our expanded research effort.”

NIEHS will invest approximately $30 million over two years on BPA-related research. This includes existing grants, the newly awarded Recovery Act grants and supplements, in-house research and NTP projects. The NTP effort is part of a larger five-year commitment to collaborate with the U.S. Food and Drug Administration’s National Center for Toxicological Research to examine long-term health outcomes resulting from developmental exposures.

BPA is a chemical used primarily in the production of polycarbonate plastics and epoxy resins. People, including children, are exposed to BPA in food and beverages when it leaches from the internal epoxy resin coatings of canned foods and also from consumer products such as polycarbonate tableware, food storage containers, water bottles and baby bottles. In 2008, NTP and NIEHS concluded that there is evidence from animal studies that BPA may be causing adverse effects. But researchers are uncertain about whether the changes seen in the animal studies would result in human health problems. For this reason, NIEHS identified BPA as a priority area.

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The innovative two-year grants provided through the Recovery Act will support human and animal studies that address many of the research gaps identified by expert scientific panels, and provide a better understanding of how this chemical may impact human health.

“We want the new grantees to be able to hit the ground running,” said Jerry Heindel, health scientist administrator at the NIEHS who oversees much of the institute’s portfolio on BPA. “Having the key players talking to one another as they begin new research efforts will stimulate collaboration, create opportunities to share resources, and encourage researchers to develop reliable and reproducible methods that will allow for a comprehensive assessment of the human health effects of BPA.”

In animal studies, there is some evidence linking BPA exposure with infertility, weight gain, behavioral changes, early onset puberty, prostate and mammary gland cancer and diabetes. For the newly funded research, two-year animal and human studies will focus on either developmental exposure or adult chronic exposures to low doses of BPA. Researchers will be looking at a number of health effects including behavior, obesity, diabetes, reproductive disorders, development of prostate, breast and uterine cancer, asthma, cardiovascular diseases and transgenerational or epigenetic effects. The 10 Recovery Act NIH Grand Opportunities grants focusing on BPA research have been awarded to:

Scott M. Belcher, University of Cincinnati

Kim Harley and **Brenda Eskenazi**, University of California, Berkeley

B. Paige Lawrence, University of Rochester, N.Y.

Gail S. Prins, University of Illinois at Chicago;
Shuk-Mei Ho, University of Cincinnati;
Kevin P. White, University of Chicago.

Beverly Sharon Rubin and **Andrew S. Greenberg**, Tufts University, Boston

Ana Soto, Tufts University, Boston

Shanna H. Swan and **Bernard Weiss**, University of Rochester

Frederick vom Saal, University of Missouri, Columbia

William Allen Ricke, University of Rochester School of Medicine and Dentistry, Rochester.

Cheryl L. Walker, University of Texas M. D. Anderson Cancer Center, Houston;
Shuk-Mei Ho, University of Cincinnati;
Michael A. Mancini, Baylor College of Medicine, Houston.

Robin Marjorie Whyatt, Columbia University Health Sciences, New York City

“Without the support of the American Recovery and Reinvestment Act, we would not have been able to expand on this research that is of such concern to so many people,” said Birnbaum. “Through this effort we will be able to provide a better perspective of the potential threat that exposure to bisphenol A poses to public health.”

More information about the NIH Recovery Act grant funding opportunities can be found at http://grants.nih.gov/recovery/.
To track the progress of HHS activities funded through the Recovery Act, visit http://www.hhs.gov/recovery.
To track all federal funds provided through the Recovery Act, visit http://www.recovery.gov.

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NTP Staff Recognized by Environmental Mutagen Society

Article by Robin Mackar, reprinted from *eFACTOR*, December 2009

Mike Shelby recieves plaque from Elizabeth Perill, a publisher of Elsevier.

Mike Shelby, Ph.D. of the National Toxicology Program was recognized by his peers at the 40th annual meeting of the Environmental Mutagen Society (EMS), October 24-28, in St Louis, Missouri. Shelby was publicly thanked and received an award for his service as a long-standing editor of the journal, Mutation Research.

Shelby received a plaque from Elizabeth Perill, a publisher at Elsevier, at the EMS meeting banquet. Perill said, “On behalf of Elsevier and the Editors I would like to extend our warm appreciation to Mike Shelby for his contributions of 30 years not only to Mutation Research, but to the field of mutation research as author, reviewer and editor. We wish him well in his future endeavors.” Shelby will retire as co-editor of Mutation Research at the end of this year.

The mission of the EMS is to promote critical scientific knowledge and research into the causes and consequences of damage to the genome and epigenome in order to inform and support national and international efforts to ensure a healthy, sustainable environment for future generations.

Shelby was appreciative of the award and said, “It’s amazing how fast three decades can go by when you are doing something you enjoy. I’ve seen the journal and the entire field grow tremendously and am thrilled that I was part of the effort.” Shelby has been working in the mutagenesis area since he received his PhD from the University of Tennessee at Knoxville in radiation mutagenesis and DNA repair. After serving as a research associate in the Biology Division at Oak Ridge National Laboratory, Shelby joined NIEHS in 1977. He started the NTP Center for the Evaluation of Risks to Human Reproduction in 1998.

Ray Tice recognized by EMS

Ray Tice, Ph.D., of the National Toxicology Program, was also recognized by EMS. Tice was the 32nd recipient of the society’s prestigious Alexander Hollaender Award. This award is conferred in recognition of outstanding contributions in the application of the principles and techniques of environmental mutagenesis to the protection of human health and for dedicated service to the Environmental Mutagen Society.

Tice was recognized “for his contributions to the development and application of the Comet and Micronucleus assays to environmental mutagenesis, biomonitoring and regulatory testing.” While accepting the award, Tice said, “I am very honored to receive this award, especially because of my personal and professional interactions with Dr. Hollaender in the 1980s.”

Tice plans to donate the cash award to the EMS Hollaender Fund, which supports workshops and training courses in countries where environmental mutagenesis and health issues are major concerns. “The Hollaender Courses have been and continue to be a unique contribution of the EMS to the international scientific community,” Tice remarked. Tice is the third NTP member to have received this award. Errol Zeiger, Ph.D. received it in 1987, followed by Mike Shelby in 1988.

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Fellow Receives Lab Animal Medicine Award

Article by Omari J. Bandele, reprinted from *eFACTOR*, January 2010


Coralie Zegre-Cannon

NIEHS Postdoctoral Fellow Coralie Zegre-Cannon, D.V.M., recently received first-place honors at the 60th annual American Association of Laboratory Animal Science (AALAS) National Meeting held Nov. 8-12 in Denver. Zegre-Cannon received the award for her poster presentation, "Evaluation of Route of Administration and Dosage of Tramadol as an Analgesic in the Rat."

The AALAS is the premier forum for the exchange of information and expertise in the care and use of laboratory animals. The AALAS National Meeting is the largest gathering of laboratory animal professionals in the world.

Zegre-Cannon works in the NTP Laboratory Animal Management (LAM) Group led by Angela King-Herbert, D.V.M. Her work involves the study of pain management in laboratory animal medicine. Zegre-Cannon identified the optimum dosage and route of administration of tramadol – an analgesic used in human and veterinary medicine – that produces the most effective analgesia in rats. These studies have led to additional evaluation of tramadol in a rat surgical model.

"The first place award was a big surprise for all of us but very welcome," stated King-Herbert.

In the spring of 2010, Zegre-Cannon will present her work at the American College of Laboratory Animal Medicine Forum. She also plans to submit a manuscript of her findings to the Journal of the American Association for Laboratory Animal Science (JAALAS) .

(Omari J. Bandele, Ph.D. is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Environmental Genomics Group.)

NTP Scientists Qualify for Toxicology Certification

Article by Eddy Ball, reprinted from *eFACTOR*, December 2009


Scott Auerbach


Matt Stout

Two National Toxicology Program (NTP) scientists – Scott Auerbach, Ph.D., and Matt Stout, Ph.D. – recently took an important step along toxicology's professional ranks by satisfying requirements for Diplomate of the American Board of Toxicology (D.A.B.T.) certification. ABT certification often offers an advantage in the job market and career advancement, and it has been associated with higher levels of compensation

In an announcement to NTP colleagues, Acting Chief of the Toxicology Branch Paul Foster, Ph.D., congratulated Auerbach and Stout for "their hard work and effort [that] has now reaped a wonderful reward."

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

Auerbach is a molecular toxicologist in the Host Susceptibility Branch headed by Acting Chief Jef French, Ph.D. He is a former NIEHS/NTP postdoctoral intramural research and training award (IRTA) fellow who earned a Ph.D. in pharmacology from the University of Washington, Seattle.

Stout is a toxicologist in the NTP Program Operations Branch headed by Acting Chief Cynthia Smith, Ph.D. He was an NIEHS postdoctoral IRTA fellow in applied toxicology and carcinogenesis in the NTP Toxicology Branch. Stout received a Ph.D. in toxicology from the University of North Carolina at Chapel Hill.

Diplomates hold initial ABT certification for 5 years and must demonstrate that they actively practice toxicology, engage in continuing education, and maintain expert knowledge in their field prior to pursuing recertification.

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NTP Board of Scientific Counselors

NTP Board of Scientific Counselors (BSC) meetings are tentatively scheduled for May 10 and June 20-21, 2010, at the NIEHS, 111 TW Alexander Drive, Research Triangle Park, NC. Draft substance profiles for three candidate substances for the 12th Report on Carcinogens (formaldehyde, glass wool fibers, cobalt tungsten carbide powders and hard metals) will undergo peer review at the June meeting. Additional details including the preliminary agendas will be posted to the NTP website as available *(http://ntp.niehs.nih.gov/go/calendar)*.

NTP Board of Scientific Counselors Technical Reports Review Subcommittee

The Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors met on November 19, 2009, at the NIEHS, Research Triangle Park, NC to peer review the findings and conclusions from six draft NTP Technical Reports using conventional rodent models. The Subcommittee made the recommendations recorded below regarding the findings and conclusions of the reports. These findings will be reported to the NTP Board of Scientific Counselors at a future meeting (see related article page 2). Additional details about the meeting are available on the NTP website *(http://ntp.niehs.nih.gov/go/15849)*.

1-Bromopropane (TR 564)

The Subcommittee accepted unanimously (9 yes, 0 no, 0 abstentions) the conclusions, *some evidence* of carcinogenic activity of 1-bromopropane in male F344/N rats, *clear evidence* of carcinogenic activity in female F344/N rats, no evidence of carcinogenic activity in male B6C3F1 mice, and *clear evidence* of carcinogenic activity in female B6C3F1 mice. The Subcommittee recommended that pancreatic islet adenoma and carcinoma (combined) be added to the conclusion in male F344/N rats and that the origin of skin neoplasms (epithelial) in male and female F344/N rats as well as the types of neoplasms (keratoacanthoma, squamous cell carcinoma and basal cell neoplasm) in male F344/N rats be added to the conclusions.

Ginseng (TR 567)

The Subcommittee accepted (6 yes, 4 no, 0 abstentions) the conclusions as written, *no evidence* of carcinogenic activity of ginseng in male and female F344/N rats or B6C3F1 mice.

Pulegone (TR 563)

The Subcommittee accepted (6 yes, 4 no, 0 abstentions) the conclusions, *no evidence* of carcinogenic activity of pulegone in male F344/N rats, and *clear evidence* of carcinogenic activity in male and female B6C3F1 mice. The Subcommittee recommended the conclusion of *clear evidence* of carcinogenic activity in female F344/N rats based on increased incidences of urinary bladder neoplasms. The Subcommittee recommended that the specific types of liver neoplasms in B6C3F1 mice that increased with treatment be reported in the conclusion.

Milk Thistle Extract (TR 565)

The Subcommittee accepted unanimously (10 yes, 0 no, 0 abstentions) the conclusions as written, *no evidence* of carcinogenic activity of milk thistle extract in male and female F344/N rats or B6C3F1 mice.

bis(2-Chloroethoxy)methane (TR 536)

The Subcommittee accepted unanimously (7 yes, 0 no, 0 abstentions) the conclusions as written, *no evidence* of carcinogenic activity of bis(2-chloroethoxy)methane in male or female F344/N rats or B6C3F1 mice.

Diethylamine (TR 566)

The Subcommittee accepted unanimously (8 yes, 0 no, 0 abstentions) the conclusions, *no evidence* of carcinogenic activity of diethylamine in male or female F344/N rats or B6C3F1 mice. The Subcommittee recommended that the nonneoplastic lesions in the cornea of male rats be added to the conclusions.

Contact Information: Dr. Lori White, Executive Secretary, NTP Office of Liaison, Policy and Review, NIH/NIEHS, P.O. Box 12233, K2-03, Research Triangle Park, NC 27709; T: (919) 541-9834, FAX: (919) 541-0295; whiteld@niehs.nih.gov

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NTP Testing Program

Request for Study Nominations

With a broad mandate to provide toxicological characterizations for chemicals and other substances of public health concern, the NTP accepts nominations for new toxicological studies at any time. Labor unions, academic scientists, federal and state agencies, industry, and the general public are welcome to make nominations for specific substances or for general issues related to potential human health hazards of occupational or environmental exposures. As available, a rationale for study should accompany the nomination along with background information describing sources of exposure and possible adverse health effects or concerns associated with exposure, the chemical name and the Chemical Abstract Service (CAS) registry number. Details about the nomination review and selection process are available on the NTP web site (http://ntp.niehs.nih.gov, select *Nominations to the Testing Program* under the heading *Testing Information*) or by contacting the NTP Office of Nomination and Selection (contact information below).

Current areas of focus in the NTP's testing program include potential hazards associated with radiofrequency radiation from cellular phones, metals, nanoscale materials, perfluorinated compounds, herbal dietary supplements, photoactive chemicals, brominated flame retardants, certain complex occupational exposures, dioxin-like compounds, contaminants of finished drinking water, and endocrine-active substances.

Contact Information: Dr. Scott A. Masten, Director, NTP Office of Nomination and Selection, NIH/NIEHS, P.O. Box 12233, MD K2-02, Research Triangle Park, NC 27709; T: (919) 541-5710; FAX: (919) 541-3647; masten@niehs.nih.gov

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Report on Carcinogens (RoC)

Scientific Review of Formaldehyde

On November 4, a ten-member, independent, scientific expert panel convened by the NTP voted unanimously to list formaldehyde as a "known human carcinogen" in the upcoming 12th Edition of the Report on Carcinogens (RoC). Currently, formaldehyde is listed in the 11th RoC as "reasonably anticipated to be a human carcinogen." The vote came after three days of presentations, public comments, and lengthy discussions of the body of literature on this widely used chemical.

The expert panel's peer review comments on the draft background document, listing recommendation, and scientific justification are now available on the RoC website (*http://ntp.niehs.nih.gov/go/29682*). The NTP invites public comment on the recommendation and scientific justification for the recommendations (74 FR 62317). Comments should be sent to the RoC Center (see contact information below) by February 8, 2010. The NTP will finalize the background document, taking into consideration the panel's recommended edits and public comments on the draft document.

Next steps in the review process include additional internal government review followed by preparation of the draft substance profile containing the NTP's listing recommendation for formaldehyde in the 12th RoC and the scientific information supporting the recommendation. The draft substance profile is tentatively scheduled for peer review at the June meeting of the NTP Board of Scientific Counselors *(see related article page 2)*.

Contact Information: Dr. Ruth M. Lunn, Report on Carcinogens Office, NIH/NIEHS, P.O. Box 12233, MD K2-14, Research Triangle Park, NC 27709; T: (919) 316-4637; FAX: (919) 541-0144; lunn@niehs.nih.gov

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NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) convened a public, expert panel meeting on December 16-18, 2009, in Alexandria, Virginia to evaluate soy infant formula.

The 14-member, independent, scientific panel reviewed and evaluated the available scientific data on soy infant formula. In their deliberations, the expert panel considered the quality and strength of the scientific evidence that soy formula or its isoflavone constituents might cause adverse effects on human development. The expert panel also identified gaps in the available scientific data on the possible effects of soy formula and suggested areas where additional research is needed.

Soy formula is an infant food made using soy protein and other components. It is fed to infants as a supplement or replacement for human milk or cow milk formula. Soy formula contains isoflavones, naturally occurring compounds found primarily in beans and other legumes including soybeans, peanuts, and chickpeas. The three main isoflavones in soy formula are genistein, daidzein, and to a smaller extent, glycitein.

The expert panel expressed minimal concern for adverse developmental effects in infants fed soy infant formula. The panel voted 10 yes, 2 no in favor of the conclusion. The two panel members voting no included one member who expressed negligible concern and one member who expressed some concern.

The expert panel used a five-level scale to express their conclusions to characterize the likelihood of an adverse human health effect resulting from exposure to soy infant formula. The concern levels range from highest to lowest:

Serious Concern	Concern	Some Concern	Minimal Concern	Negligible Concern

A Federal Register notice is scheduled for publication on January 15, 2009 announcing the availability of the final expert panel report for a 45-day public comment period.

Contact Information: Dr. Kristina Thayer, Acting Director CERHR, NIH/NIEHS, P.O. Box 12233, MD K2-04, Research Triangle Park, NC 27709; T: (919) 541-5021; FAX: (919) 316-4511; thayer@niehs.nih.gov

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

Evaluation of Endocrine Disruptor Screening Assays: Expert Panel Nominations and Data Submissions Requested

NICEATM requests nominations of expert scientists to serve on an international, independent, scientific review panel to assess the validation status of two *in vitro* assays for their usefulness and limitations in determining whether chemicals interact with estrogen receptors *in vitro*. NICEATM also requests submission of relevant data for consideration by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the panel.

NICEATM in collaboration with ICCVAM will convene the panel as part of the ICCVAM technical evaluation of the scientific validity of an *in vitro* stably transfected estrogen receptor (ER) transcriptional activation (TA) Assay (LUMI-CELL® ER assay, XDS, Inc.) and an *in vitro* cell proliferation assay (CertiChem, Inc., MCF-7 Cell

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Proliferation assay). Each assay has been evaluated using protocols to detect ER agonist and antagonist activity. The panel will consider all available data generated using these assays or from *in vivo* or *in vitro* assessments for the 78 reference substances recommended by ICCVAM for the validation of *in vitro* ER and androgen receptor binding and TA test methods (see PDF document available at: *http://iccvam.niehs.nih.gov/docs/endo_docs/EDAddendFinal.pdf*). Where appropriate, data will be used to assess the validity of the assays and to aid in the development of performance standards for these test methods.

NICEATM invites the submission of relevant *in vitro* and *in vivo* data and information for the ICCVAM-recommended reference substances or for other substances for which data exist from the LUMI-CELL ER assay and the CertiChem MCF-7 Cell Proliferation assay. NICEATM also invites nominations of scientists with relevant knowledge and experience to serve on the panel. Areas of relevant expertise include, but are not limited to, biostatistics, cellular biology, endocrinology, molecular genetics, regulatory toxicology, reproductive toxicology, and test method validation. NICEATM should receive the data and nominations by January 11, 2010; data submitted after this date will be considered in the evaluation, where feasible.

Information about the NICEATM-sponsored validation studies, as well as instructions on how to submit data and nominations, is available at: *http://iccvam.niehs.nih.gov/methods/endocrine/ED-ERassay.htm*.

South Korea Establishes Center for Validation of Alternative Toxicological Methods

The Korean Center for the Validation of Alternative Methods (KoCVAM) was established recently in South Korea as part of the National Institute of Food and Drug Safety (NIFDS) in the Korean Food and Drug Administration (KFDA). In recognition of the establishment of KoCVAM, the inaugural KoCVAM International Symposium was held at Seoul National University on November 3. Dr. William Stokes, NICEATM Director, gave the keynote address entitled “Validation and Regulatory Acceptance of Alternative Methods for Safety Testing: Recent Progress and Future Directions.” He emphasized the need for high quality scientific validation studies for proposed new safety test methods as a prerequisite for regulatory acceptance and use, and highlighted new technologies and scientific advances anticipated to support future development of more predictive safety tests.

While in Seoul, Dr. Stokes visited the Korean FDA and met with the Deputy Commissioner of the KFDA and the Director General of the NIFDS. He also participated in a KoCVAM Colloquium to discuss areas for potential collaboration on international validation studies and evaluation activities and to share current processes used to coordinate international validation studies and test method evaluations. Plans were made for regular communications and possible future joint validation studies and test method evaluations.

NICEATM Director Delivers Plenary Lecture at Annual Meeting of Japanese Society for Alternatives to Animal Experiments

Dr. William Stokes delivered the keynote plenary lecture for the 22nd Annual Meeting of the Japanese Society for Alternatives to Animal Experiments (JSAAE) held at Osaka University in Osaka, Japan, on November 13-15. His presentation, “Advancing Laboratory Animal Welfare and Public Health Science: The Role of Innovative Refinement, Reduction, and Replacement Strategies,” was presented to over 300 scientists representing government, academe, and industry. The topic of the meeting was “The 3Rs: Refinement and then Reduction and Replacement.”

While in Japan, Dr. Stokes participated in an international workshop on dermal safety of cosmetics and chemicals where he presented the recent ICCVAM evaluation of several new versions and applications of the Local Lymph Node Assay. He delivered an update on NICEATM-ICCVAM activities and procedures at the advisory committee meeting of the Japanese Center for the Validation of Alternative Methods (JaCVAM) and met with JaCVAM staff, including Director Hajime Kojima, to discuss joint validation and evaluation activities with NICEATM and ICCVAM. One of these activities is an ongoing JaCVAM validation study of the Bhas 42 cell transformation assay as a screening test to identify potentially carcinogenic substances. Dr. Stokes met with the management team for this study in his role as the NICEATM liaison.

International Meeting on the Murine Local Lymph Node Assay

The Organisation for Economic Co-operation and Development (OECD) convened an expert consultation meeting on October 20-22, 2009, to evaluate modifications to the murine Local Lymph Node Assay (LLNA), a test method

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to detect potential skin sensitizing substances. This meeting held at CPSC headquarters in Bethesda, MD included scientists from NIEHS, EPA, FDA, and CPSC, as well as experts from industry and other stakeholder organizations. NICEATM and ICCVAM co-hosted the meeting.

The expert group reviewed proposed revisions to the OECD test guideline for the LLNA, TG 429, that were based on recommendations recently forwarded to U.S. Federal agencies by ICCVAM. The proposed revisions include approaches that can reduce the number of animals in each test by up to 40%, an improved guidance on establishing the highest test dose, and performance standards that can be used to expedite the validation of modified versions of the LLNA.

The expert group also reviewed drafts of two new proposed test guidelines for nonradioisotopic versions of the LLNA. These test methods, the LLNA:DA (that measures ATP content) and LLNA:BrdU-ELISA (that measures BrdU incorporation), do not require radioisotopes to measure lymphocyte proliferation as the traditional LLNA does. Having OECD test guidelines for these test methods will enable more widespread use, especially where use of radioisotopes is prohibited or restricted. The draft test guidelines are based on ICCVAM's evaluation of the two test methods. ICCVAM recommendations on their usefulness and limitations in the United States are being finalized and will be forwarded to U.S. Federal agencies in early 2010.

The new and updated test guidelines are being revised to incorporate comments made at the October meeting. The revised draft test guidelines will then be sent to OECD member countries for review and comment.

Scientific Workshop on Vaccine Potency and Safety Testing

A public workshop on alternative methods to reduce, refine, or replace the use of animals in vaccine potency and safety testing will be held September 14-16, 2010, at the William H. Natcher Conference Center at the National Institutes of Health in Bethesda, MD. More information about the workshop will be posted on the NICEATM-ICCVAM website as it becomes available.

Vaccines represent a vital and cost-effective tool in the prevention of numerous infectious diseases. The increasing occurrence of antibiotic-resistant strains of bacterial diseases, the emergence of novel viral illnesses, the public health implications of infections in livestock, and the priority given by the World Health Organization to the eradication of a number of diseases are factors that underscore the importance of vaccines. Currently, animal tests are required for lot-release potency and safety testing of many vaccines. These tests generally require large numbers of animals and may involve unrelieved pain and distress. Accordingly, efforts have increased to develop alternative methods that reduce, refine, or replace the use of animals for vaccine potency and safety testing.

Call for Nominations and Submissions of Test Methods with Potential Regulatory Applications

NICEATM and ICCVAM welcome nominations and submissions of new or modified alternative safety testing methods with the potential to reduce, refine, or replace the use of animals while maintaining or increasing protection of human health, animal health, and the environment.

- A test method submission is made to ICCVAM on a test method where validation studies characterizing the method's usefulness and limitations for a specific regulatory application have been completed.
- A test method nomination consists of a proposal to ICCVAM for review and evaluation where the information required for a complete test method submission is not available. Examples are (1) test methods for which validation studies have been completed but a complete submission package has not been prepared, (2) test methods proposed for prevalidation or validation studies, and (3) test methods recommended for a workshop or other activity.

NICEATM encourages sponsors wishing to propose nominations or submissions of promising test methods to contact them for information and guidance on preparing proposals. Information about nominations and submissions to ICCVAM is available on the NICEATM-ICCVAM website at *http://iccvam.niehs.nih.gov/SuppDocs/submission.htm* or by contacting NICEATM.

Contact Information: Dr. William S. Stokes, Director, NICEATM, NIH/NIEHS, P.O. Box 12233, MD K2-16, Research Triangle Park, NC 27709; T: (919) 541-2384; FAX (919) 541-0947; niceatm@niehs.nih.gov

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