UPDATE
National Toxicology Program

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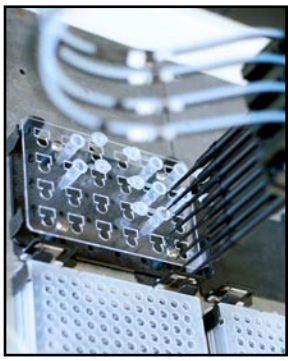
National Institute of Environmental
Health Sciences NIH-DHHS

What's Inside:

Trans-Agency Agreement to Transform Environmental Health Protection

Article by Robin Mackar and Eddy Ball, reprinted from eFACTOR*, March 2008*



Recent advances in science and technology now make it possible to improve how scientists evaluate the health risks posed by chemicals found in the environment. During a press teleconference on February 14, NIH Director Elias A. Zerhouni, M.D., and NIEHS Acting Director Sam Wilson, M.D., joined with leading scientists from NIEHS, the National Human Genome Research Institute (NHGRI) and the U.S. Environmental Protection Agency (EPA) to announce a new collaborative agreement intended to take advantage of new technologies and shift the protocol for toxicity assessments from laboratory animal studies to more cell- based tests.

The concept behind this agreement was highlighted in paper published as the Policy Forum of the Feb. 15, 2008 issue of the journal *Science*. The article was jointly authored by NHGRI Director Francis Collins, M.D., Ph.D., Assistant Administrator of EPA's Office of Research and Development George Gray, Ph.D., and John Bucher, Ph.D., associate director of the National Toxicology Program (NTP), which is headquartered at NIEHS.

NIEHS and NHGRI signed a five-year Memorandum of Understanding (MOU) with the EPA to use the NIH Chemical Genomics Center's (NCGC) high-speed, automated screening robots to test suspected toxic compounds using cells and isolated molecular targets instead of laboratory animals. This new, trans-agency collaboration is anticipated to generate data more relevant to humans; expand the number of chemicals that are tested; and reduce the time, money and number of animals involved in testing. Full implementation of the anticipated paradigm shift in toxicity testing will require

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Plan Expedites Alternatives to Animal Testing

Article by Robin Mackar, reprinted from eFACTOR*, March 2008*

The new Five-Year Plan to further reduce, refine and replace the use of animals in research and regulatory testing, commonly referred to as the *3Rs*, was unveiled at a symposium February 5 in Bethesda, MD, marking the 10-year anniversary of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). A cornerstone of the federal government's five-year plan is the formation of partnerships with industry and other national and international stakeholders to achieve measurable progress.

NIEHS is one of the fifteen federal regulatory and research agencies that make up ICCVAM. One of the speakers at the symposium was William Stokes, D.V.M., director of the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).

"We've made great progress in the past decade, and with

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NEXT

Upcoming Events

June 11-12, 2008
NTP BSC Technical Reports Review Subcommittee
Radisson Hotel Research Triangle Park
150 Park Drive
Research Triangle Park, NC

June 18-19, 2008
Scientific Advisory Committee on Alternative Toxicological Methods
Radisson Hotel Research Triangle Park
150 Park Drive
Research Triangle Park, NC

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validation of the new approaches, a substantial effort that could consume many years.

The MOU builds on the experimental toxicology expertise of the NTP, the quantitative high-throughput screening technology at NCGC, managed by NHGRI, and the computational toxicology capabilities at the EPA's recently formed National Center for Computational Toxicology (NCCT).

The agreement addresses opportunities for coordination in four basic areas related to achieving the toxicant testing goals: identification of toxicity pathways; selection of chemicals for testing; analysis and interpretation of data; and outreach to scientific and regulatory communities. The collective budget is yet to be determined.

"The experimental and computational expertise required to transform toxicology is an enormous undertaking and too great for any of our existing organizations to accomplish alone," added Bucher. "This collaborative approach allows us to draw on our individual strengths and establishes a long-term, multiple U.S. federal agency commitment." NTP will contribute thousands of compounds for testing. NTP's animal toxicology expertise will be utilized, along with a large database of the chemicals' effects on animals, with which the new cell-based data will be compared.

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The Agreement in Context

The MOU and the plans articulated in the *Science* article provide a framework to implement the long-range vision outlined in the 2007 National Research Council (NRC) report, Toxicity Testing in the 21st Century: A Vision and a Strategy, which proposed a collaborative effort across the toxicology community to rely less on animal studies and more on *in vitro* tests using human cells and cellular components to identify chemicals with toxic effects. Importantly, the strategy calls for improvements in dose-response research, which will help predict toxicity at exposures that humans may encounter.

Housed at the NIH Chemical Genomics Center, these Kalypsys robots perform precision plate handling for high throughput screening. *(Photo courtesy of NHGRI*

Data collection to determine chemical toxicity currently relies heavily on whole-animal tests. The growing number of new chemicals, adding to a backlog of thousands that have yet to be thoroughly assessed, high testing costs and public unease with animal testing led to the search for alternate toxicology testing methods. Quantitative high throughput screening (qHTS), developed at NCGC, increases the rate at which chemicals are tested, and profiles compounds over a wide range of concentrations.

These qualities make the new qHTS technology ideal for toxicology testing, with the potential for advancing the goal of more accurate and timely public health decisions. According to the *Science* article, the screening of >100,000 per day with HTS performed on automated platforms is routine in drug discovery.

By pooling resources and forming a working partnership, the agreement overcomes the resource limitations of a single agency, builds on existing expertise and avoids the need to create a new administrative and support structure for the effort.

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Plan Expedites Alternatives to Animal Testing

the help of our partners we can do even more to increase the pace of developing and introducing alternative methods," he said of the group's accomplishments. "By incorporating recent advances in science and technology, new alternative test methods can be developed that will benefit animal welfare by reducing, refining and replacing animal use, and that will benefit public health by ensuring continued or improved protection of human and animal health and the environment."

Stokes was one of nearly 200 scientists, public attendees, advocates, media representatives and invited guests participating in a scientific symposium. ICCVAM is a permanent interagency committee composed of representatives from agencies which use, generate or disseminate toxicological information. "ICCVAM has a proven track record of thoroughly reviewing test methods and has established an excellent blueprint for advancing the *3Rs*, and for advancing the health and safety of our nation as well," said Marilyn Wind, Ph.D., deputy associate executive director of the Consumer Product Safety Commission and the chair of ICCVAM.

ICCVAM does not conduct research itself. Instead, the committee promotes the development, validation and regulatory acceptance of scientifically sound new, revised and alternative testing methods brought forth by government and industry labs that protect human and animal health and the environment. Based on its evaluation of new methods, ICCVAM makes recommendations about their usefulness to federal regulatory agencies.

Traditionally, chemicals, consumer products, medical devices and new drugs are tested on animals to predict toxicity on humans. Alternative test methods are those that accomplish one or more of the *3Rs* so animals experience less pain and distress, or replace animals with non-animal systems.

Stokes highlighted some of the progress made since ICCVAM was formed, including the evaluation of more than 185 test methods since its inception in 1997. Many of these methods need further development and validation before they are ready for regulatory consideration. However, several are now in widespread use around the world for routine safety testing, resulting in notable reduction and refinement of animal use.

Stokes said ICCVAM will emphasize the use of new technologies to develop predictive systems that would be less reliant or not at all reliant on animals. Technologies touted by the National Research Council and the NTP, including high throughput screening

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"A central component of federal effort will explore the use of high throughput screening assays in toxicology," Collins explained. "Such assays allow for the testing of thousands to hundreds of thousands of chemicals a day to determine their possible toxic effect." NCGC is part of a larger Molecular Libraries Imaging Program within the NIH Roadmap for Medical Research. It was designed to advance research on molecules from which most medicines marketed today are derived.

"As our detailed research strategy continues to develop, we will welcome the participation of other federal partners, as well as interested public and private sector organizations, to make this vision of 21st century toxicology a reality," Gray observed. The EPA's engagement in this collaboration is part of its ToxCast™ program – an initiative launched in 2007 to integrate advances in computers, genomics and cellular biology into the agency's chemical toxicity evaluation procedures.

Also participating in the press conference were Robert Kavlock, Ph.D., director of the National Center for Computational Toxicology, Office of Research and Development, EPA, Christopher Austin, director of the NIH Chemical Genomics Center, and Raymond Tice, Ph.D., acting chief of the NTP Biomolecular Screening Branch.

NTP Board of Scientific Counselors to Meet

On June 11-12, 2008, the NTP Board of Scientific Counselors (NTP BSC) will meet in public at the Radisson Hotel Research Triangle Park in Research Triangle Park, NC. Among the topics tentatively on the agenda are peer review of the draft NTP Brief on bisphenol A, information about NTP studies of DNA-based therapies, and a discussion of testing program nominations for dimorpholinodiethyl ether, 2-ethylhexyl-*p*-methoxycinnamate, 4, 7, 1 0-trioxatridecane-1,13-diamine, and tetravalent and pentavalent vanadium compounds), as well as proposed research projects on furan and melamine and cyanuric acid.

Other topics tentatively planned for the meeting include development of criteria for evaluating outcomes in reproductive, developmental, and immunotoxicology studies as well as updates on current programmatic activities in high throughput screening and host susceptibility. The preliminary agenda, roster, draft documents, public comments and other information, as available, will be posted on the NTP BSC meeting website http://ntp.niehs.nih.gov/go/165. The NTP is also making plans to webcast the meeting over the Internet http://www.niehs.nih.gov/news/video/live.

Contact Information: Dr. Barbara Shane, Executive Secretary, NTP Office of Liaison, Policy and Review, NIH/NIEHS, P.O. Box 12233, MD A3-01, Research Triangle Park, NC 27709; T: (919) 541-4253; shane@niehs.nih.gov

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

Draft NTP Brief on Hydroxyurea

CERHR released the draft NTP Brief on hydroxyurea on March 17, 2008, and invites public comments on the report through May 1 (73FR14251). Hydroxyurea is a drug used to treat cancer, sickle cell disease, and thalassemia. It is the only treatment for sickle cell disease used in children, aside from blood transfusion and, in severe cases, stem cell transplantation. The draft brief presents NTP's preliminary conclusions on whether or not hydroxyurea is a reproductive or developmental hazard in exposed people.

The draft brief is based on the CERHR Expert Panel Report on Hydroxyurea, public comments received on that report, and any new relevant scientific literature available since the expert panel meeting held on January 24-26, 2007. The draft brief and other materials related to this review are available on the CERHR website http://cerhr.niehs.nih.gov/chemicals/hydroxyurea/hydroxyurea.html and public comments received will be posted to this site. NTP will consider the public comments as if finalizes the brief, which will be released as part of the NTP-CERHR Monograph on hydroxyurea later in 2008.

Draft NTP Brief on Bisphenol A

The draft NTP Brief on bisphenol A was released on April 15, 2008, and public comments are invited through May 16. Bisphenol A is a compound widely used in the manufacture of polycarbonate bottles, food containers, items such as CDs, and resins that are used to line food cans. It can also be found in some infant formula bottles and children's toys. The draft brief presents the NTP's scientific review of bisphenol A and the resulting conclusions related to human reproduction and the development of children.

The draft brief is available on the CERHR website http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.html and public comments received will be posted on the website. After public input and scientific peer review at the NTP Board of Scientific Counselors meeting in June (article sharing this page), the final brief will be released as a part of the NTP-CERHR Monograph on bisphenol A in late summer 2008.

Contact Information: Dr. Michael D. Shelby, Director CERHR, NIH/NIEHS, P.O. Box 12233, MD EC-32, Research Triangle Park, NC 27709, T: (919) 541-3455; FAX: (919) 316-4511; shelby@niehs.nih.gov

SACATM to Meet in June

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) will meet on June 18-19, 2008, at the Radisson Hotel Research Triangle Park, 150 Park Drive in Research Triangle Park, NC.

This meeting is open to the public and public comment, both written and oral, is welcome on all agenda topics. Details about the meeting, including registration information and agenda topics, will be announced in the Federal Register and posted on the NTP website http://ntp.niehs.nih.gov/go/7441

Contact Information: Dr. Lori White, Executive Secretary, NTP Office of Liaison, Policy and Review, NIH/NIEHS, P.O. Box 12233, MD A3-01, Research Triangle Park, NC 27709; T: (919) 541-9834; whiteld@niehs.nih.gov

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

ICCVAM Celebrates 10th Anniversary with Scientific Symposium and Release of the NICEATM-ICCVAM Five-Year Plan

ICCVAM recently celebrated its 10-year anniversary with a scientific symposium "Celebrating Ten Years of Advancing Public Health and Animal Welfare with Sound Science: Envisioning New Directions in Toxicology." The symposium was held February 5, 2008, at U.S. Consumer Product Safety Commission Headquarters in Bethesda, MD and attended by over 100 people.

Attendees represented many of the ICCVAM stakeholder groups, including Federal agencies, academia, industry, international organizations and the animal welfare community. Distinguished speakers addressed ICCVAM's role in advancing toxicology testing in the 21st Century and representatives from ICCVAM stakeholder groups participated in a panel discussion with the theme "Test Method Research, Development, Translation and Validation: The Way Forward for ICCVAM and its Stakeholders."

As a part of the symposium, NICEATM and ICCVAM also presented their Five-Year Plan. The plan describes how NICEATM and ICCVAM, in partnership with Federal agencies, will promote the research, development, translation and validation of alternative test methods over the next five years. Acceptance and implementation of scientifically valid methods will further reduce, refine and replace the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health and the environment.

More information about the symposium can be found on the website: http://iccvam.niehs.nih.gov/meetings/10thAnnivSymp/10thAnnivSymp.htm. For the press release describing the NICEATM-ICCVAM Five-Year Plan go to: http://www.niehs.nih.gov/news/releases/2008/animaltest.cfm. More information concerning the Five-Year Plan can be found here: http://iccvam.niehs.nih.gov/docs/5yearplan.htm.

Scientists Meet to Discuss Non-Animal Testing and More Humane Endpoints in Animal Testing for Acute Systemic Toxicity

The workshop "Acute Chemical Safety Testing: Advancing *In Vitro* Approaches and Humane Endpoints for Systemic Toxicity Evaluations" held February 6-7, 2008, at the NIH brought together over 100 attendees representing 6 countries. It provided a forum for discussing how to advance the development of *in vitro* test methods for predicting acute systemic toxicity and identify earlier, more humane endpoints that could be incorporated into existing chemical safety tests.

The workshop included a review of the state-of-the-science and discussions toward the identification of knowledge gaps in the understanding of key pathways involved in acute systemic toxicity. Attendees were asked to provide input on how the identification of *in vivo* key pathways associated with acute systemic toxicity could be used to advance the development of predictive *in vitro* methods and earlier more humane endpoints. The workshop was co-organized by NICEATM-

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Scientists Meet to Discuss Non-Animal Testing and More Humane Endpoints in Animal Testing for Acute Systemic Toxicity

ICCVAM, the European Centre for the Validation of Alternative Methods, and the Japanese Center for the Validation of Alternative Methods and was open to the public at no cost. More information on the workshop and a brief workshop summary are available on the NICEATM-ICCVAM website at http://iccvam.niehs.nih.gov/meetings/AcuteToxWksp08/AcuteToxWksp08.htm

Report on Carcinogens

Expert Panel Recommends Listing Status for Captafol and *ortho*-Nitrotoluene

At the first meeting for review of candidate substances to the 12th RoC, the expert panel first reviewed the draft background document for each candidate substance and then made a recommendation on its listing status in the 12th RoC. The panel recommended that captafol be listed as "reasonably anticipated to be a human carcinogen" based on sufficient evidence of carcinogenicity in experimental animals and strong supporting mechanistic evidence. Captafol (CAS RN: 2425-06-1) is a broad-spectrum fungicide that was widely used in the United States prior to the mid 1980s on fruits, vegetables, and other plants, as well as on timber products. The panel recommended that *ortho*-nitrotoluene be listed as "reasonably anticipated to be a human carcinogen" based on sufficient evidence of carcinogenicity in experimental animals and supporting mechanistic evidence. *ortho*-Nitrotoluene (CAS RN: 88-72-2) is used to synthesize agricultural and organic chemicals, explosives, azo and sulfur dyes, and dyes for cotton, wool, silk, leather, and paper.

The meeting, which was open to the public, was held on October 15-16, 2007, at the Chapel Hill Sheraton Hotel in Chapel Hill, NC. The background documents and expert panel report containing the recommendations on the listing status for captafol and *ortho*-nitrotoluene and scientific support (Expert Panel Reports Part B) were released for public comment on March 3, 2008 (73FR12736). Comments are being accepted through April 24 and those received will be posted on the RoC website. Information about this meeting is available on the RoC website or by contacting the RoC office (contact information below).
http://ntp.niehs.nih.gov/go/29682

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

Meeting on the Validation Status of New Versions and New Applications of the Murine Local Lymph Node Assay

NICEATM, in collaboration with ICCVAM, convened an independent scientific peer review panel to evaluate new versions and new applications for the Murine Local Lymph Node Assay (LLNA). The meeting, which was open to the public, was held March 4-6, 2008, at the U.S. Consumer Product Safety Commission in Bethesda, MD. The LLNA is an alternative test method used to determine the allergic contact dermatitis potential of chemicals and products.

Specifically, the panel reviewed:

- The validation status of three modified LLNA test method protocols that use non-radioactive probe chemicals
- The validation status of a LLNA limit dose procedure
- The usefulness of the LLNA for testing mixtures, aqueous solutions, and metals (applicability domain for the LLNA)
- The usefulness of the LLNA to determine potency categories for substances that cause allergic contact dermatitis
- Revised draft recommended performance standards for the LLNA

The panel peer-reviewed draft documents for each topic and evaluated whether established validation and acceptance criteria were appropriately addressed. They also commented on the extent that the docu-

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NTP Staff Publications: October – December 2007

The URL to the article is provided although in some incidences access may require a subscription to the journal.

NIEHS

J. T. Auman, G. A. Boorman, R. E. Wilson, G. S. Travlos and R. S. Paules (2007). "Heat map visualization of high-density clinical chemistry data." *Physiological Genomics* 31(2): 352-356.
PMID: 17652165
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17652165
DOI: 10.1152/physiolgenomics.00276.2006

D. R. Bell, S. Clode, M. Q. Fan, A. Fernandes, P. M. D. Foster, T. Jiang, G. Loizou, A. MacNicoll, B. G. Miller, M. Rose, L. Tran and S. White (2007). "Relationships between tissue levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), mRNAs, and toxicity in the developing male Wistar(Han) rat." *Toxicological Sciences* 99(2): 591-604.
PMID: 17656490
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17656490
DOI: 10.1093/toxsci/kfm179

W. A. Boyd, S. J. McBride and J. H. Freedman (2007). "Effects of Genetic Mutations and Chemical Exposures on Caenorhabditis elegans Feeding: Evaluation of a Novel, High-Throughput Screening Assay." *PLoS ONE* 2(12): e1259.
PMID: 18060055
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18060055
DOI: 10.1371/journal.pone.0001259

P. R. Bushel, A. N. Heinloth, J. Li, L. Huang, J. W. Chou, G. A. Boorman, D. E. Malarkey, C. D. Houle, S. M. Ward, R. E. Wilson, R. D. Fannin, M. W. Russo, P. B. Watkins, R. W. Tennant and R. S. Paules (2007). "Blood gene expression signatures predict exposure levels." *Proceedings of the National Academy of Sciences of the United States of America* 104(46): 18211-18216
PMID: 17984051
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17984051
DOI: 10.1073/pnas.0706987104

M. A. Carey, J. W. Card, J. W. Voltz, S. J. Arbes Jr, D. R. Germolec, K. S. Korach and D. C. Zeldin (2007). "It's all about sex: gender, lung development and lung disease." *Trends in Endocrinology and Metabolism* 18(8): 308-313.
PMID: 17764971
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17764971
DOI: 10.1016/j.tem.2007.08.003

P. C. Chan, R. C. Sills, G. E. Kissling, A. Nyska and W. Richter (2007). "Induction of thyroid and liver tumors by chronic exposure to 2-methylimidazole in F344/N rats and B6C3F1 mice." *Archives of Toxicology*
PMID: 17924096
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17924096
DOI: 10.1007/s00204-007-0249-7

L. J. Chen Ferguson, E. H. Lebetkin, E. I. Nwakpuda and L. T. Burka (2007). "Metabolism and disposition of n-butyl glycidyl ether in F344 rats and B6C3F1 mice." *Drug Metabolism and Disposition* 35(12): 2218-2224.
PMID: 17875671
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17875671
DOI: 10.1124/dmd.107.016931

L. J. Chen and L. T. Burka (2007). "Chemical and enzymatic oxidation of furosemide: Formation of pyridinium salts." *Chemical Research in Toxicology* 20(12): 1741-1744
PMID: 17914885
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17914885
DOI: 10.1021/tx700262z

Y. X. Cui, S. J. McBride, W. A. Boyd, S. Alper and J. H. Freedman (2007). "Toxicogenomic analysis of Caenorhabditis elegans reveals novel genes and pathways involved in the resistance to cadmium toxicity." *Genome Biology* 8(6)
PMID: 17592649
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17592649
DOI: 10.1186/gb-2007-8-6-r122

J. K. Dunnick, G. Kissling, D. K. Gerken, M. A. Vallant and A. Nyska (2007). "Cardiotoxicity of Ma Huang/caffeine or ephedrine/caffeine in a rodent model system." *Toxicologic Pathology* 35(5): 657-664
PMID: 17676524
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17676524
DOI: 10.1080/01926230701459978

J. K. Dunnick, K. A. Thayer and G. S. Travlos (2007). "Inclusion of biomarkers for detecting perturbations in the heart and lung and lipid/carbohydrate metabolism in National Toxicology Program Studies." *Toxicological Sciences* 100(1): 29-35
PMID: 17490986
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17490986
DOI: 10.1093/toxsci/kfm113

D. E. Gray, D. Messer, A. Porter, B. Hefner, D. Logan, R. K. Harris, A. P. Clark, J. A. Algaier, J. D. Overstreet and C. S. Smith (2007). "Analysis of flavonol aglycones and terpenelactones in Ginkgo biloba extract: A comparison of high-performance thin-layer chromatography and column high-performance liquid chromatography." *Journal of Aoac International* 90(5): 1203-1209
PMID: 17955963
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17955963

J. F. Hardisty, M. R. Elwell, H. Ernst, P. Greaves, H. Kolenda-Roberts, D. E. Malarkey, P. C. Mann and P. A. Tellier (2007). "Histopathology of hemangiosarcomas in mice and hamsters and liposarcomas/fibrosarcomas in rats associated with PPAR agonists." *Toxicologic Pathology* 35(7): 928-941
PMID: 18098039
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18098039
DOI: 10.1080/01926230701748156

A. B. Moore, L. Castro, L. Yu, X. Zheng, X. Di, M. I. Sifre, G. E. Kissling, R. R. Newbold, C. D. Bortner and D. Dixon (2007). "Stimulatory and inhibitory effects of genistein on human uterine leiomyoma cell proliferation are influenced by the concentration." *Human Reproduction* 22(10): 2623-2631
PMID: 17725991
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17725991
DOI: 10.1093/humrep/dem185

J. P. Morrison, H. Satoh, J. Foley, J. L. Horton, J. K. Dunnick, G. E. Kissling and D. E. Malarkey (2007). "N-ethyl-N-nitrosourea (ENU)-induced meningiomatosis and meningioma in p16INK4a /p19ARF tumor suppressor gene-deficient mice." *Toxicologic Pathology* 35(6): 838-845
PMID: 17943659
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17943659
DOI: 10.1080/01926230701584130

J. A. Patz, H. K. Gibbs, J. A. Foley, J. V. Rogers and K. R. Smith (2007). "Climate change and global health: Quantifying a growing ethical crisis." *EcoHealth* 4(4): 397-405
PMID: 17762687
http://www.scopus.com/scopus/inward/record.url?eid=2-s2.0-37349048091&partnerID=40&rel=R7.0.0
DOI: 10.1007/s10393-007-0141-1

M. V. Smith, C. R. Miller, M. Kohn, N. J. Walker and C. J. Portier (2007). "Absolute estimation of initial concentrations of amplicon in a real-time RT-PCR process." *BMC Bioinformatics* 8
PMID: 17956631
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17956631
DOI: 10.1186/1471-2105-8-409

M. M. Taylor, W. S. Stokes, R. Bajuscak, M. Serdula, K. L. Siegel, B. Griffin, J. Keiser, L. Agate, A. Kite-Powell, D. Roach, N. Humbert, K. Brusuelas and S. S. Shekar (2007). "Mobilizing mobile medical units for hurricane relief: The United States Public Health Service and Broward County Health Department response to hurricane Wilma, Broward county, Florida." *Journal of Public Health Management and Practice* 13(5): 447-452
PMID: 17762687
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17762687
DOI: 10.1097/01.PHH.0000285195.39179.7d

N. J. Walker, K. Yoshizawa, R. A. Miller, A. E. Brix, D. M. Sells, M. P. Jokinen, M. E. Wyde, M. Easterling and A. Nyska (2007). "Pulmonary lesions in female Harlan Sprague-Dawley rats following two-year oral treatment with dioxin-like compounds." *Toxicology Pathology* 35(7): 880-9
PMID: 18098034
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18098034
DOI: 10.1080/01926230701748396

C. G. Woods, O. Kosyk, B. U. Bradford, P. K. Ross, A. M. Burns, M. L. Cunningham, P. Qu, J. G. Ibrahim and I. Rusyn (2007). "Time course investigation of PPAR?- and Kupffer cell-dependent effects of WY-14,643 in mouse liver using microarray gene expression." *Toxicology and Applied Pharmacology* 225(3): 267-277
PMID: 17950772
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17950772
DOI: 10.1016/j.taap.2007.08.028

K. Yoshizawa, A. Heatherly, D. E. Malarkey, N. J. Walker and A. Nyska (2007). "A critical comparison of murine pathology and epidemiological data of TCDD, PCB126, and PeCDF." *Toxicologic Pathology* 35(7): 865-879
PMID: 18098033
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18098033
DOI: 10.1080/01926230701618516

NCTR

C.R. Cederroth, M. Vinciguerra, F. Kuhne, R. Madani, D. R. Doerge, T. J. Visser, M. Foti, F. Rohner-Jeanrenaud, J. D. Vassalli and S. Nef (2007). "A phytoestrogen-rich diet increases energy expenditure and decreases adiposity in mice." *Environmental Health Perspectives* 115(10): 1467-1473
PMID: 17938737
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17938737
DOI: 10.1289/ehp.10413

G.G. da Costa, M. M. Marques, X. Fu, M. I. Churchwell, Y. P. Wang, D. R. Doerge and F. A. Beland (2007). "Effect of N,N-didesmethyltamoxifen upon DNA adduct formation by tamoxifen and alpha-hydroxytamoxifen." *Cancer Letters* 257(2): 191-198
PMID: 17765393
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17765393
DOI: 10.1016/j.canlet.2007.07.014

S. A. Ferguson, F. J. Cisneros, J. P. Hanig and K. J. Berry (2007). "Oral treatment with ACCUTANE does not increase measures of anhedonia or depression in rats." *Neurotoxicol Teratol* 29(6): 642-51
PMID: 17933491
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17933491
DOI: 10.1016/j.ntt.2007.09.003

C. E. Hotchkiss, C. Wang and W. Slikker Jr (2007). "Effect of prolonged ketamine exposure on cardiovascular physiology in pregnant and infant rhesus monkeys (Macaca mulatta)." *Journal of the American Association for Laboratory Animal Science* 46(6): 21-28
PMID: 17994669
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17994669

I. P. Pogribny, T. V. Bagnyukova, V. P. Tryndyak, L. Muskhelishvili, R. Rodriguez-Juarez, O. Kovalchuk, T. Han, J. C. Fuscoe, S. A. Ross and F. A. Beland (2007). "Gene expression profiling reveals underlying molecular mechanisms of the early stages of tamoxifen-induced rat hepatocarcinogenesis." *Toxicol Appl Pharmacol* 225(1): 61-9
PMID: 17706260
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17706260
DOI: 10.1002/rcm.3295

E. Tareke, J. F. Bowyer and D. R. Doerge (2007). "Quantification of rat brain neurotransmitters and metabolites using liquid chromatography/electrospray tandem mass spectrometry and comparison with liquid chromatography/electrochemical detection." *Rapid Communications in Mass Spectrometry* 21(23): 3898-3904
PMID: 17979107
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17979107
DOI: 10.1002/rcm.3295

X. Zou, N. Sadovova, T. A. Patterson, R. L. Divine, C. E. Hotchkiss, S. F. Ali, J. P. Hanig, M. G. Paule, W. Slikker, Jr. and C. Wang (2008). "The effects of l-carnitine on the combination of, inhalation anesthetic-induced developmental, neuronal apoptosis in the rat frontal cortex." *Neuroscience* 151(4): 1053-65
PMID: 18201836
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18201836
DOI: 10.1016/j.neuroscience.2007.12.013

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Meeting on the Validation Status of New Versions and New Applications of the Murine Local Lymph Node Assay

ments supported draft recommendations by ICCVAM on the proposed test method protocols and uses and on the revised draft LLNA performance standards. Additional information about this peer review, including the draft documents and public comments, are available on the NICEATM-ICCVAM website http://iccvam.niehs.nih.gov/meetings/LLNAPanelMtg08/LLNAPanelMtg08.htm.

Contact Information: Dr. William S. Stokes, Director, NICEATM, NIH/NIEHS, P.O. Box 12233, MD EC-32, Research Triangle Park, NC 27709: T: (919) 541-2384; FAX: (919) 541-0947; iccvam@niehs.nih.gov

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Plan Expedites Alternatives to Animal Testing

techniques that can screen large numbers of potentially hazardous chemicals at one time and toxicogenomics, for example, will be studied and incorporated where they can to provide more accurate and timely public health decisions.

A high priority for ICCVAM, Stokes added, will be to focus on evaluating alternatives to test methods that use a large number of animals or that can involve significant pain and stress, including safety tests for ocular (eye) injuries, dermal (skin) damage, acute poisoning and tests for biologics such as vaccines. Additional priorities include safety tests to determine if products and chemicals may cause other adverse health effects such as cancer, birth defects, infertility and allergic responses.

The five-year plan was developed over a 12-month period with multiple opportunities for input, including a public Town Meeting held in June 2006. The NICEATM-ICCVAM Five-Year Plan is available online.