UPDATE
National Toxicology Program

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NTP Marks Milestones in Alternatives to Animal Testing

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

When the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) convened its annual meeting June 18-19 at the Research Triangle Park Radisson Hotel, there seemed to be a general sense of satisfaction about the accomplishments being made by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). The meeting provided an opportunity for federal agencies to discuss the progress each was making in implementing the NICEATM-ICCVAM Five-Year Plan, celebrate accomplishments, enjoy some lively debate and discuss future directions.

After some brief welcoming and introductory remarks by ICCVAM Chair Marilyn Wind, Ph.D., and NTP Associate Director John Bucher, Ph.D., on behalf of NTP Acting Director Samuel Wilson, M.D., the meeting was turned over to the SACATM Chair, James Freeman, Ph.D.

The meeting commenced with two presentations, one by NTP scientist Bill Stokes, D.V.M., the executive director of ICCVAM and director of NICEATM, and one by Kim Boekelheide, Ph.D., of Brown University.

Stokes opened with a progress report on ICCVAM and NICEATM activities during the past year including the tenth anniversary celebration of ICCVAM in February, which coincided with release of the committee's Five-Year Plan. The plan outlines strategies for researching, developing, translating, validating and promoting new and revised non-animal and other alternative assays for integration of the three Rs — reduction, refinement, and replacement of animal testing — into Federal agency testing programs through 2012.

As ICCVAM looks forward, Stokes said, the committee also reflected on accomplishments over the past decade. "Seventeen alternative methods have been accepted or endorsed by US federal agencies since 1999… [and] include alternative methods that can be used to reduce and refine animal use for the most commonly conducted product safety tests," he explained. "Twelve of these are non-animal methods, [and] ten of those seventeen are based on ICCVAM technical evaluations and recommendations."

Stokes then discussed the recent acceptance of two new alternative methods recommended by ICCVAM to reduce live animal use for ocular safety testing. The two alternative test methods, the bovine corneal opacity and permeability (BCOP) assay and the isolated chicken eye (ICE) assay, are the first scientifically valid alternative methods to gain regulatory acceptance for ocular safety testing.

Stokes also emphasized that increasing international cooperation will be instrumental in helping the testing community adopt more alternative methods over the next five years. Stokes was pleased to acknowledge that a representative of the European Centre for Validation of Alternative Methods (ECVAM) and the

director of the Japanese Center for the Validation of Alternative Methods (JaCVAM) were attending the meeting, and noted the increasing collaborations among the three organizations, as well as ICCVAM participation in several international forums.

Boekelheide finished out the morning with a summary of the National Research Council report, *Toxicity Testing in the 21st Century*. He discussed why the NRC panel was established, the Panel's charge and its recommendations, as well as some of his own personal views on the need for a paradigm shift for toxicity testing.

"This is not something that anyone expects to happen overnight," Boekelheide said of the implementation. "The Panel was thinking in the 20- to 50-year time frame for this to come about."

He pointed out that one of the most attractive features of the report is its focus on mechanisms of action and toxicity pathways rather than phenotypic responses. "It's the new science, and I think that's an important driver."

The afternoon sessions focused on short individual presentations by agency representatives on the role they are playing related to the implementation of the Five-Year Plan.

Attending her first meeting of SACATM, Norka Ruiz Bravo, Ph.D., NIH deputy director for Extramural Research, highlighted some of the scientific projects NIH is supporting in relation to the NICEATM-ICCVAM Five-Year Plan, including the development of non-mammalian models such as zebra fish. Bravo also talked about the significance of the Memorandum of Understanding signed between NIH and EPA to screen chemicals more rapidly, the value of microarray gene chips in research efforts and the advantages of 3-D tissue models to help accelerate discovery and safety evaluations of therapeutic agents.

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NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC) will meet on November 20-21, 2008, at the NIEHS, 111 TW Alexander Drive, Research Triangle Park, NC. Preliminary agenda items include nominations and research concepts for the NTP testing program, updates on the high throughput screening initiative, a presentation on the toxicology of DNA-based therapies, and reports from working groups convened to evaluate criteria for use in evaluating outcomes in NTP studies of the immune system, reproduction, or development. Additional details about the meeting, including preliminary agenda and roster, will be posted on the NTP website as available (http://ntp.niehs.nih.gov/go/calendar). This meeting is open to the public.

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

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In recognition of their work on the NICEATM-ICCVAM Five-Year Plan, 12 individuals received an NIH Director's Group Award on July 21:

NIEHS — William Stokes, D.V.M., Sheila Newton, Ph.D., Deborah McCarley, Raymond Tice, Ph.D.

Other ICCVAM Agency Representatives— Marilyn Wind, Ph.D., CPSC: Suzanne Fitzpatrick, Ph.D., FDA; David Hattan, Ph.D., FDA; Abigail Jacobs, Ph.D., FDA; Jodie Kulpa-Eddy, D.V.M., USDA; Alan Poland, M.D., NCI; Amy Rispin, Ph.D., EPA; Margaret Snyder, Ph.D., NIH, Office of the Director

Upcoming Events

September 11-12, 2008

High Throughput Screening Approaches for Toxicology Meeting
NIEHS, 111 TW Alexander Dr., Research Triangle Park, NC

October 14-17, 2008

NIH Research Festival
Natcher Center, NIH
Bethesda, MD

November 20-21, 2008

NTP Board of Scientific Counselors Meeting
NIEHS, 111 TW Alexander Dr., Research Triangle Park, NC

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

NTP Report on Carcinogens (RoC)

Scientific Review of Styrene

On July 21-22, 2008, an expert panel met at the Radisson Hotel Research Triangle Park, NC to evaluate styrene, which is nominated for possible listing in the 12th RoC. Styrene is a monomer used worldwide in the production of polymers that are incorporated into products such as rubber, plastic, insulation, fiberglass, pipes, automobile parts, food containers, and carpet backing. After receiving oral public comments from a number of groups, the expert panel carried out an in-depth review of the draft background document on styrene identifying edits to the text and additional references for inclusion. Following completion of the peer review, the expert panel discussed the scientific evidence regarding the carcinogenicity of styrene and recommended (8 yes/ 2 no) that styrene be listed in the 12th RoC as reasonably anticipated to be a human carcinogen based upon sufficient evidence from studies in experimental animals and limited evidence from studies in humans. Next, the NTP will solicit public comment on the expert panel's listing recommendation and scientific justification through the Federal Register and finalize the background document taking into consideration the panel's recommended edits and public comments. Information about this meeting and the review of styrene is available on the RoC website (http://ntp.niehs.nih.gov/go/29679) or by contacting the RoC Office (see below).

Final Background Documents on Captafol and *ortho*-Nitrotoluene Available

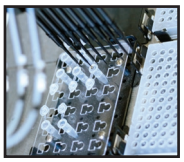
The public meeting for the scientific review of captafol and *ortho*-nitrotoluene took place on October 15-16, 2007, at the Chapel Hill Sheraton Hotel, Chapel Hill, NC. At this meeting, the expert panel reviewed the draft background document for each substance and made recommendations regarding their listing status in the 12th RoC. The final RoC background documents, peer review comments, and listing recommendations and scientific justification are posted on the RoC website (http://ntp.niehs.nih.gov/go/29682) and available in hardcopy or on CD from the RoC Office (contact information below).

Recommendations on Listing Status of Aristolochic Acid Related Exposures and Riddelliine

The public meeting for scientific review of aristolochic acid related exposures and riddelliine took place on January 24-25, 2008, at the Sheraton Hotel, Chapel Hill, NC. At this meeting, the expert panel reviewed the draft background documents for aristolochic acid related exposures and riddelliine and made recommendations regarding their listing status. The recommendations and scientific justification for listing status are available on the RoC website (http://ntp.niehs.nih.gov/go/29682). It is anticipated that the final background documents on aristolochic acid and riddelliine will be posted on the RoC website by September 2008.

Contact Information: Dr. Ruth M. Lunn, Report on Carcinogens 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

NTP High Throughput Screening Meeting



The National Toxicology Program has issued a Request for Information (RFI): High Throughput Screening Approaches for Toxicology. The RFI seeks information and comments on the identification and selection of critical cellular toxicity pathways for interrogation in cell-based high throughput screens and recommendations on particular molecular targets within these critical cellular toxicity pathways that are most informative for profiling the pathways, both in cell-based and biochemical assay formats. In addition to information on cellular pathways and targets, the NTP seeks information on technologies and assay systems that might be used in the development of a comprehensive approach to high throughput toxicity screening.

A public meeting to provide information to the NTP High Throughput Screening (HTS) Initiative (http://ntp.niehs.nih.gov/go/28213) on HTS assays, critical cellular toxicity pathways, and molecular targets through oral presentations and a question and answer session will be held on September 11-12, 2008, at the NIEHS, Rodbell Auditorium, 111 TW Alexander Drive, Research Triangle Park, NC. Details about the meeting, including registration information and agenda topics, have been announced in the Federal Register and the NIH Grants and Contracts listing, and posted on the NTP website (URL: http://ntp.niehs.nih.gov/go/32908). See also FedBizOpps Notice (URL: https://www.fbo.gov/notices/08ae6af478214489efe7c4ce870fce34)

Additional information on the HTS Initiative is available at the following weblink: http://ntp.niehs.nih.gov/go/28213

Contact Information: Kristine Witt, NTP HTS Initiative, NIH/NIEHS, P.O. Box 12233, MD EC-32, Research Triangle Park, NC 27709; T: (919) 541-2761; FAX: (919) 316-4511; witt@niehs.nih.gov

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NTP Scientists to Participate in 2008 NIH Research Festival

Dr. John (Jef) French will chair a research symposium *Genetic Susceptibility – The Link between Environmental Exposure and Human Disease* at the October 14-17, 2008 NIH Research Festival (http://researchfestival.nih.gov/). This is an annual event, open to the public. Environmental exposures can have a significant impact on the development of human disease depending upon an individual's inherited genotype of environmentally responsive genes. This symposium will explore NIH research using genetically defined mouse models, which can provide both insight and corroborate how environmental factors and genetic susceptibilities affect development of major human diseases including cancer and heart and respiratory diseases. The symposium will be held 2-4 pm, October 14, in Balcony B, Natcher Conference Center, NIH. Invited talks include:

- *Genetic susceptibility to environmental lung disease: a translational investigation*, Dr. Steve Kleeberger, NIEHS
- *Inherited susceptibility to breast cancer progression and metastasis*, Dr. Kent W. Hunter, NCI
- *The interaction of genetics and epigenetics in susceptibility to NF1-associated nervous system tumors*, Dr. Karlyne M. Reilly, NCI
- *Studies of environmental and genetic factors in cardiac disease using mouse model systems*, Dr. June Dunnick, NIEHS/NTP
- *Genetic Susceptibility to DNA strand break damage, loss of heterozygosity (genomic instability), and cancer*, Dr. John E. (Jef) French, NIEHS/NTP

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

Draft NTP Brief on BPA Gets Public Comment and Peer Review

On June 11 the NTP Board of Scientific Counselors (BSC), supplemented with ad hoc experts, met at the Radisson Triangle Park, Research Triangle Park, NC to peer review the draft NTP Brief on Bisphenol A (BPA). The Draft Brief details the NTP's assessment of the risks of BPA exposure for affecting human reproduction and development in humans. In preparing the Draft Brief, the NTP considered the Expert Panel Report issued in November 2007, public comments on that report, and new relevant scientific literature published subsequent to the expert panel evaluation.

The meeting began with an overview of the NTP evaluation of BPA by Dr. Michael Shelby, CERHR director. This presentation was followed by oral comments on the Draft Brief from interested groups and individuals, in-person or by conference call. Following an in-depth discussion of the evidence including public comments, the BSC agreed with the overall conclusions in the Draft Brief including some concern for neural and behavioral effects and effects on the prostate gland in fetuses, infants, and children at current human exposures to BPA. But the BSC recommended that the NTP modify the level of concern from some concern to minimal concern for effects in the mammary gland and an earlier age for puberty in females. The five levels of concern used by the NTP are from highest to lowest: serious concern, concern, some concern, minimal concern, and negligible concern. The peer review report and NTP response to the peer review comments will be posted on the NTP website (http://ntp.niehs.nih.gov/go/9741) in the near future. The NTP will consider the peer review comments and public comments in finalizing the Brief for an anticipated late summer 2008 release.

Contact Information: Dr. Michael D. Shelby, Director CERHR, NIH/NIEHS,
P.O. Box 12233, MD EC-32, Research Triangle Park, NC 27709,
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shelby@niehs.nih.gov

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NTP Articles Make Top 10 List

Journal articles from the NTP Cellular and Molecular Pathology Branch were recently recognized for being among those published in *Toxicology Pathology* with the most full-text accesses from January 2008-April 2008 on Sage Journals Online.

Full-text Accesses*	Article
1,195	**Susan A. Elmore** Invited Review: Apoptosis: A Review of Programmed Cell Death *Toxicologic Pathology*, 35:495-516 Jun 1 2007.
978	**Gail Pearse**** Normal Structure, Function and Histology of the Thymus *Toxicologic Pathology*, 34:504-514 Aug 1 2006.
962	**Mark F. Cesta** Normal Structure, Function, and Histology of Mucosa-Associated Lymphoid Tissue *Toxicologic Pathology*, 34:599-608 Aug 1 2006.
935	**Gregory S. Travlos** Normal Structure, Function, and Histology of the Bone Marrow *Toxicologic Pathology*, 34:548-565 Aug 1 2006.
673	**Gregory S. Travlos** Histopathology of Bone Marrow *Toxicologic Pathology*, 34:566-598 Aug 1 2006.
617	**Abraham Nyska**** Invited Review: Oxidation of Biological Systems: Oxidative Stress Phenomena, Antioxidants, Redox Reactions, and Methods for Their Quantification *Toxicologic Pathology*, 30:620-650 Oct 1 2006.
551	**Susan A. Elmore** Enhanced Histopathology of the Spleen *Toxicologic Pathology*, 34:648-655 Aug 1 2006.
512	**Mark F. Cesta** Normal Structure, Function and Histology of the Spleen *Toxicologic Pathology*, 34:455-465 Aug 1 2006.

** Full-text accesses are the combined sum of reference views and PDF full-text downloads*
*** Former NIEHS staff*

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

Test Method Recommendations for Alternative, Non-Animal Ocular Toxicity Test Methods Accepted by Agencies

In November 2007, NICEATM, on behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), forwarded the *ICCVAM Test Method Evaluation Report:* In Vitro *Ocular Toxicity Test Methods for Identifying Severe Irritants and Corrosives* (NIH Publication 07-4517) to U.S. Federal agencies for regulatory and other acceptance considerations. These are the first non-animal test methods for ocular safety testing reviewed and recommended by ICCVAM and now they have been accepted or endorsed by all applicable Federal agencies.

ICCVAM recommended that two of the evaluated methods be used in a tiered testing strategy to determine ocular hazards, and that substances, which test positive, can be classified as ocular corrosives or severe irritants without further testing in animals. With acceptance by applicable agencies, these *in vitro* test methods may now be used instead of conventional tests for certain regulatory testing purposes. Use of these methods will reduce the number of animals used for safety testing to determine permanent or temporary damage to the eye.

ICCVAM will now seek international adoption of these test methods by the Organization of Economic Cooperation and Development (OECD). This adoption will allow these test methods to be used in the other 29 OECD member countries including Japan, Canada, and most countries in the European Union (EU). There is considerable interest in these methods in Europe due to the impending 2009 EU ban on the use of animals for testing cosmetic ingredients and the chemical testing that will be required by the EU REACH (Registration, Evaluation, Authorization and Restriction of Chemical substances) regulation that took effect in June 2007.

The transmittal letters and agency responses can be found on the NICEATM-ICCVAM website at: http://iccvam.niehs.nih.gov/methods/ocutox/ivocutox/ocu_recommend.htm. There are also links to the final background review documents, the ICCVAM Test Method Evaluation report, and a June 2008 NIH press release announcing the acceptance of the methods by Federal agencies.

Report from the LLNA Peer Review Panel Now Available

NICEATM, in collaboration with ICCVAM, sponsored an international independent scientific peer review to evaluate modifications and new applications for the Murine Local Lymph Node Assay (LLNA). This meeting took place March 4-6 at the U.S. Consumer Product Safety Commission Headquarters in Bethesda, MD.

The LLNA is an alternative test method that can be used to determine the allergic contact dermatitis potential of chemicals and products. 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 use of the LLNA to test mixtures, aqueous solutions, and metals (applicability domain for the LLNA)
- The use of the LLNA to determine potency (potential for allergic contact dermatitis hazard)
- Revised draft recommended performance standards for the LLNA

The panel peer reviewed the draft documents for each topic and evaluated the extent that established validation and acceptance criteria had been appropriately addressed. They also commented on the extent that the review documents supported draft ICCVAM recommendations on proposed test method protocols and uses and on the revised draft LLNA performance standards.

The report, Independent Scientific Peer Review Panel Report: Validation Status of New Versions and Applications of the Murine Local Lymph Node Assay: *A Test Method for Assessing the Allergic Contact Dermatitis Potential of Chemicals and Products*, was published in May. ICCVAM will consider the panel's recommendations as well as public comments and comments from its scientific advisory committee as it develops final recommendations on the LLNA. ICCVAM recommendations on the evaluated methods are expected by fall 2008.

The report is available on the NICEATM-ICCVAM website at http://iccvam.niehs.nih.gov/methods/immunotox/llna_PeerPanel.htm along with links to the draft documents reviewed by the panel and other meeting information.

Recommendations for Alternative, Non-Animal Acute Toxicity Test Methods Forwarded to Agencies

NICEATM, on behalf of ICCVAM, forwarded the *ICCVAM Test Method Evaluation Report:* In Vitro *Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Tests* (NIH Publication No. 07-4519) to U.S. Federal agencies in February 2008 for regulatory consideration. ICCVAM recommended that the *in vitro* basal cytotoxicity test methods examined in a joint ICCVAM/ECVAM validation study be considered before using animals for acute oral toxicity testing and that the methods should be used where determined appropriate. Data from the test methods can be used in a weight-of-evidence approach for determining starting doses for *in vivo* studies. Using these *in vitro* methods is expected to reduce the number of animals required for each toxicity test. ICCVAM concluded that the *in vitro* test methods are not sufficiently accurate to replace animals for regulatory hazard classification purposes.

A link to the ICCVAM Test Method Evaluation Report and final background review documents can be found on the NICEATM-ICCVAM website (http://iccvam.niehs.nih.gov/methods/acutetox/inv_nru_announce.htm). Agency responses to the ICCVAM recommendations are being posted on the website as they arrive and should all be received by August 28, 2008.

Progress on Validation Studies of *In Vitro* Methods to Identify Potential Endocrine Disruptors

Currently, no adequately validated *in vitro* test methods exist to identify chemicals with the potential to disrupt normal function of endocrine receptors. In 2005, LUMI-CELL,® an *in vitro* test method that uses cultured cells to identify substances that induce or inhibit transcriptional activation (TA) of estrogen receptor (ER)-mediated pathways, was nominated to ICCVAM for evaluation. A NICEATM-sponsored multi-phased international validation study of the LUMI-CELL test method is in progress. Study activities are focused on optimizing the protocol and demonstrating intralaboratory repeatability within laboratories, and reproducibility of assay results within and between laboratories. By identifying and resolving sources of variability early in the validation process, this approach should produce a standardized protocol for a reproducible and sensitive ER agonist/antagonist TA assay that is suitable for international regulatory use. To this end, ICCVAM is participating in the development of an OECD Test Guideline applicable to the LUMI-CELL test method.

The results from the validation study will be used to develop a high quality, *in vitro* ER TA database. This database may be used to develop performance standards for evaluating the usefulness and limitations of functionally and mechanistically similar test methods. Performance standards define the basis against which to demonstrate that new proprietary (i.e., copyrighted, trademarked, registered) and nonproprietary test methods, which are considered functionally and mechanistically similar to an accepted test method, have sufficient relevance and reliability for specific testing purposes.

More information about the LUMI-CELL validation study can be found on the NICEATM-ICCVAM website (http://iccvam.niehs.nih.gov/methods/endocrine/end_eval.htm).

New Listing on U.S. Regulatory Acceptance of Alternative Methods

A table summarizing the regulatory acceptance of alternative toxicological methods has been posted on the NICEATM-ICCVAM website (http://iccvam.niehs.nih.gov/about/accept/US.htm). It contains links to pages describing relevant NICEATM-ICCVAM test method evaluation activities and comparing the acceptance of alternative methods in the United States and Europe.

Since ICCVAM's establishment, Federal regulatory agencies have approved or endorsed 17 alternative methods including 10 alternative test methods based on technical evaluations by ICCVAM. Included are 12 non-animal methods and 5 methods that use fewer animals and reduce the potential for discomfort. Several methods can be used for the 4 most commonly conducted safety tests including tests to identify substances that can cause poisoning (acute oral toxicity), irritation and chemical burns to the skin or eyes, and allergic skin reactions. Use of these accepted methods will significantly reduce and refine the use of animals for regulatory testing.

Contact Information: Dr. William S. Stokes, Director, NICEATM, NIH/NIEHS,
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niceatm@niehs.nih.gov

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NTP Staff Publications January - March 2008

Badr MZ, Shnyra, A, Zoubine, M, Norkin, M, Herndon, B, Quinn, T, Miranda, RN, **Cunningham, ML** and Molteni, A (2007). "Phthalate-induced liver protection against deleterious effects of the Th1 response: A potentially serious health hazard." *PPAR Research*
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18566640
DOI: http://dx.doi.org/10.1155/2007/49671

Bucher JR (2008). "NTP: New initiatives, new alignment." *Environmental Health Perspectives* 116(1): A14-A15.
PubMed: Not available.
DOI: http://dx.doi.org/10.1289/ehp.11100

Chan PC and Fu, PP (2007). "Toxicity of Panax genseng - An herbal medicine and dietary supplement." *Journal of Food and Drug Analysis* 15(4): 416-427.
PubMed: Not available.
DOI: Not available.

Chan PC, Hill, GD, **Kissling, GE** and Nyska, A (2008). "Toxicity and carcinogenicity studies of 4-methylimidazole in F344/N rats and B6C3F1 mice (Archives of Toxicology DOI 10.1007/s00204-007-0222-5)." *Archives of Toxicology* 82(1): 45.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/17619857
DOI: http://dx.doi.org/10.1007/s00204-007-0222-5

Chan PC, Xia, QS and Fu, PP (2007). "Ginkgo biloba leave extract: Biological, medicinal, and toxicological effects." *Journal of Environmental Science and Health Part C-Environmental Carcinogenesis & Ecotoxicology Reviews* 25(3): 211-244.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/17763047
DOI: http://dx.doi.org/10.1080/10590500701569414

Chen LJ and **Burka, LT** (2007). "Chemical and enzymatic oxidation of furosemide: Formation of pyridinium salts." *Chemical Research in Toxicology* 20(12): 1741-1744.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/17914885
DOI: http://dx.doi.org/10.1021/tx700262z

Collins FS, Gray, GM and **Bucher, JR** (2008). "Toxicology – Transforming environmental health protection." *Science* 319(5865): 906-907.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18276874
DOI: http://dx.doi.org/10.1126/science.1154619

Dong J, **Boyd, WA** and **Freedman, JH** (2008). "Molecular Characterization of Two Homologs of the Caenorhabditis elegans Cadmium-Responsive Gene cdr-1: cdr-4 and cdr-6." *Journal of Molecular Biology* 376(3): 621-633.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18177893
DOI: http://dx.doi.org/10.1016/j.jmb.2007.11.094

Fu PP, Xia, QS, Guo, L, Yu, HT and **Chan, PC** (2008). "Toxicity of kava kava." *Journal of Environmental Science and Health Part C-Environmental Carcinogenesis & Ecotoxicology Reviews* 26(1): 89-112.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18322868
DOI: http://dx.doi.org/10.1080/10590500801907407

Gargas, ML, **Collins, B**, Fennell, TR, Gaudette Jr, NF and Sweeney, LM (2008). "Disposition of styrene-acrylonitrile (SAN) trimer in female rats: Single dose intravenous and gavage studies." *Toxicology Letters* 178(1): 1-8.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18384980
DOI: http://dx.doi.org/10.1016/j.toxlet.2008.01.016

Golub, MS, Collman, GW, **Foster, PMD**, Kimmel, CA, Meyts, ERD, Reiter, EO, Sharpe, RM, Skakkebaek, NE and Toppari, J (2008). "Public health implications of altered puberty timing." *Pediatrics* 121: S218-S230.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18245514
DOI: http://dx.doi.org/10.1542/peds.2007-1813G

Guindon, KA, **Foley, JF, Maronpot, RR** and Massey, TE (2008). "Failure of catalase to protect against aflatoxin B1-induced mouse lung tumorigenicity." *Toxicology and Applied Pharmacology* 227(2): 179-183.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18155117
DOI: http://dx.doi.org/10.1016/j.taap.2007.10.015

Hardisty, JF, Elwell, MR, Ernst, H, Greaves, P, Kolenda-Roberts, H, **Malarkey, DE**, Mann, PC and Tellier, PA (2007). "Histopathology of hemangiosarcomas in mice and hamsters and liposarcomas/fibrosarcomas in rats associated with PPAR agonists." *Toxicologic Pathology* 35(7): 928-941.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18098039
DOI: http://dx.doi.org/10.1080/01926230701748156

Jacobson-Kram, D, Mattison, D, **Shelby, M**, Slikker, W, **Tice, R** and **Witt, K** (2008). "Methylphenidate and chromosome damage." *Cancer Letters* 260(1-2): 216-218.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18055105
DOI: http://dx.doi.org/10.1016/j.canlet.2007.10.017

Johnson, K (2008). "Introduction to rodent cardiac imaging." *ILAR Journal* 49(1): 27-34.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18172331
DOI: Not available.

Kang-Sickel, JC, Fox, DD, Nam, TG, Jayaraj, K, Ball, LM, **French, JE**, Klapper, DG, Gold, A and Nylander-French, LA (2008). "S-Arylcysteine-Keratin Adducts as Biomarkers of Human Dermal Exposure to Aromatic Hydrocarbons." *Chem Res Toxicol* 21(4): 852-858.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18361511
DOI: http://dx.doi.org/10.1021/tx7003773

Kim, YS, Hong, SK, **Herbert, R**, Ju, YB, Collins, JB, Grissom, SF and Jetten, AM (2008). "Kruppel-like zinc finger protein Glis2 is essential for the maintenance of normal renal functions." *Molecular and Cellular Biology* 28(7): 2358-2367.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18227149
DOI: http://dx.doi.org/10.1128/MCB.01722-07

Lo, YC, Liu, Y, Lin, YC, Shih, YT, Liu, CM and **Burka, LT** (2008). "Neuronal effects of 4-t-Butylcatechol: A model for catechol-containing antioxidants." *Toxicology and Applied Pharmacology* 228(2): 247-255.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18190940
DOI: http://dx.doi.org/10.1016/j.taap.2007.12.001

Longnecker, MP, **Smith, CS, Kissling, GE**, Hoppin, JA, Butenhoff, JL, Decker, E, Ehresman, DJ, Ellefson, ME, Flaherty, J, Gardner, MS, Langlois, E, Leblanc, A, Lindstrom, AB, Reagen, WK, Strynar, MJ and Studabaker, WB (2008). "An interlaboratory study of perfluorinated alkyl compound levels in human plasma." *Environ Res*
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18295197
DOI: http://dx.doi.org/10.1016/j.envres.2008.01.005

Melnick, RL, Thayer, KA and **Bucher, JR** (2008). "Conflicting views on chemical carcinogenesis arising from the design and evaluation of rodent carcinogenicity studies." *Environmental Health Perspectives* 116(1): 130-135.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18197312
DOI: http://dx.doi.org/10.1289/ehp.9989

Newbold, RR, Padilla-Banks, E, Jefferson, WN and Heindel, JJ (2008). "Effects of endocrine disruptors on obesity." *International Journal of Andrology* 31(2): 201-207.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18315718
DOI: http://dx.doi.org/10.1111/j.1365-2605.2007.00858.x

Ruhlen, RL, Howdeshell, KL, Mao, J, Taylor, JA, Bronson, FH, **Newbold, RR**, Welshons, WV and vom Saal, FS (2008). "Low phytoestrogen levels in feed increase fetal serum estradiol resulting in the "fetal estrogenization syndrome" and obesity in CD-1 mice." *Environmental Health Perspectives* 116(3): 322-328.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18335098
DOI: http://dx.doi.org/10.1289/ehp.10448

Smith, MV, Miller, CR, Kohn, M, **Walker, NJ** and Portier, CJ (2007). "Absolute estimation of initial concentrations of amplicon in a real-time RT-PCR process." *BMC Bioinformatics* 8.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/17956631
DOI: http://dx.doi.org/10.1186/1471-2105-8-409

Stout, MD, Herbert, RA, Kissling, GE, Suarez, F, Roycroft, JH, Chhabra, RS and **Bucher, JR** (2008). "Toxicity and carcinogenicity of methyl isobutyl ketone in F344N rats and B6C3F1 mice following 2-year inhalation exposure." *Toxicology* 244(2-3): 209-219.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18178301
DOI: http://dx.doi.org/10.1016/j.tox.2007.11.014

Walker, NJ, Yoshizawa, K, Miller, RA, Brix, AE, Sells, DM, Jokinen, MP, **Wyde, ME**, Easterling, M and Nyska, A (2007). "Pulmonary lesions in female Harlan Sprague-Dawley rats following two-year oral treatment with dioxin-like compounds." *Toxicologic Pathology* 35(7): 880-889.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18098034
DOI: http://dx.doi.org/10.1080/01926230701748396

Witt, KL, Livanos, E, **Kissling, GE**, Torous, DK, **Caspary, W, Tice, RR** and Recio, L (2008). "Comparison of flow cytometry- and microscopy-based methods for measuring micronucleated reticulocyte frequencies in rodents treated with nongenotoxic and genotoxic chemicals." *Mutation Research-Genetic Toxicology and Environmental Mutagenesis* 649(1-2): 101-113.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/17869571
DOI: http://dx.doi.org/10.1016/j.mrgentox.2007.08.004

Xia, M, Huang, R, **Witt, KL**, Southall, N, Fostel, J, Cho, MH, Jadhav, A, **Smith, CS**, Inglese, J, Portier, CJ, **Tice, RR** and Austin, CP (2008). "Compound cytotoxicity profiling using quantitative high-throughput screening." *Environmental Health Perspectives* 116(3): 284-291.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18335092
DOI: http://dx.doi.org/10.1289/ehp.10727

Yoshizawa, K, Heatherly, A, **Malarkey, DE, Walker, NJ** and Nyska, A (2007). "A critical comparison of murine pathology and epidemiological data of TCDD, PCB126, and PeCDF." *Toxicologic Pathology* 35(7): 865-879.
PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18098033
DOI: http://dx.doi.org/10.1080/01926230701618516

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