CAAT*feed*

CAAT turns 30!

For more than 30 years, the Johns Hopkins Center for Alternatives to Animal Testing has worked to promote the development, use, and validation of the 3Rs of alternatives. CAAT celebrated by hosting the opening reception at the 8th World Congress on Alternatives and Animal Use in the Life Sciences, which took place August 21-25 in Montréal, Canada.

CAAT is not only a year older but also busier and more productive than ever. We are proud to announce that CAAT is the recipient of a $ 6 million grant from the National Institutes of Health (NIH) to pioneer potentially revolutionary new methods for toxicological testing to improve human health and reduce animal testing. CAAT Director Thomas Hartung, MD, PhD, and his team at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, along with partner Agilent Technologies and noted scientists from government and industry, received the funding for a consortium to develop a new technological methodology for mapping the molecular pathways of toxicity within cells. Funding for the project comes from the Common Fund's NIH Director's Transformative Research Projects Program (R01), which is designed to support exceptionally innovative, high risk, original and/or unconventional research that has the potential to create or overturn fundamental scientific paradigms. See: http://altweb.jhsph.edu/news/current/caatnihgrant.html

Dr Hartung and Dr Hogberg were also awarded a $ 1.2 million project "*Identification of pathways of developmental neurotoxicity for high throughput testing by metabolomics*" by US FDA. There exists a critical concern that exposures to drugs and chemicals during early life contribute to the increasing incidence of neurodevelopmental disorders in children, such as lowered IQ, learning disabilities, autism and attention deficit and hyperactivity disorder (ADHD). The developing brain is more susceptible to substance-induced injury compared to the adult brain due to the complex developmental processes, the absence of a functional blood/brain-barrier and a diminished ability to detoxify chemicals. Demanding animal tests have been devised, but because of low frequencies of hazardous substances and manifestations, as well as complex underlying mechanisms, limitations of current approaches are enormous. The area is therefore of key interest for new approaches, as outlined in the NRC vision document for a toxicology in the 21st century and the critical path initiative. In a 6-year project including organization of two international conferences, promising models and prototypic test substances have been identified. Extending our recent metabolomics and genomics approaches, a systems toxicology approach now shall be applied, in order to identify and validate critical pathways of toxicity (PoT). PoT-specific reporter gene models shall then be established allowing higher test throughput.

To carry out the extensive array of projects now under way, CAAT has recruited the following new team members:

– Dr Liang Zhao, a Research Analyst, will be largely responsible for the application of different types of mass spectrometers in proteomics and metabolomics.
– Dr Martin Stephens, Senior Research Associate, will coordinate the activities of the newly developed Evidence-based Toxicology Collaboration (EBTC).
– Dr Mounir Bouhifd, a Research Associate, will work in the area of metabolomics, setting up the workflow of the testing facility activities.
– Dr Andre Kleensang will work as a Research Associate in the Department of Environmental Health Sciences. His main responsibilities will be to combine various data-rich omics approaches to identify pathways of toxicity and develop and implement novel tools for pathway of toxicity identification and validation.

Dr Hartung also has been named Editor-in-Chief of *Frontiers in Predictive Toxicity*. The Frontiers Research Foundation (FRF) is a Swiss-registered not-for-profit organization. The FRF has a social mission to enhance research knowledge societies. A core strategy of the FRF is to support equal opportunity open-access research publishing. See: http://www.frontiersin.org/predictive_toxicity

CAAT recently partnered with ILSI/HESI Developmental and Reproductive Toxicology (DART) to sponsor a workshop on Testicular Toxicology In Vitro Models, held in Baltimore, USA in October, 2011. The workshop brought together experts in testis physiology and toxicology with tissue engineers to brainstorm ways of creating environments *in vitro* that might be more conducive to maintaining spermatogenesis, with the goal of finishing with ideas for two to seven models that could feasibly be tried in the near future.

CAAT honors four awardees at World Congress in Montréal

The CAAT Recognition Award, presented at every World Congress, honors an organization or individual that has made an outstanding contribution to the field of the 3Rs, the development of alternative methods, or the field of *in vitro* science. The 2011 recipients of this award are Dr Kevin Crofton and Dr Manfred Liebsch.

Dr Kevin Crofton was chosen from a list of international nominees for an exceptional body of work in the field of neurotoxicology, especially in the area of developmental neurotoxicology (DNT). Dr Crofton is an Acting Assistant Director in the National Health and Environmental Effects Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina. He has worked as a toxicologist at EPA since 1986, receiving Scientific and Technological Achievement Awards and a Gold Medal for Commendable Public Service.

Dr Crofton's interests and expertise include areas such as developmental neurotoxicity, the cumulative risk of thyroid disruptors, and development of alternative testing methods. He served as the Developmental Neurotoxicity Team Lead for many years with the goal of fostering the development of alternative models for screening chemicals for developmental neurotoxicity. His current efforts include development of *in vitro* and alternative methods for detecting thyroid disrupting chemicals.

Dr Manfred Liebsch was selected from a list of international nominees for outstanding expertise in and dedication to the assessment, validation, and promotion of alternative methods. Dr Liebsch is the Scientific Director of Germany's Federal Institute for Risk Assessment (BfR) and Head of the "Centre of Alternative Methods to Animal Experiments" (ZEBET) unit at the BfR. He has served as Main Contractor, Co-coordinator, Participant, or Consultant on a variety of successful validation studies on alternative *in vitro* methods, both at the national and the European level. His work has focused on the fields of topical toxicity (eye- and skin-irritation and corrosion, phototoxicity, and skin absorption), and ecotoxicology (acute aquatic toxicity). Dr Liebsch also provides Expert Consultancy in the validation of new toxicological methods for hazard identification in National, European, and International Working Groups, including the ECVAM Scientific Advisory Board, the OECD Test Guidelines Program, and ISO 194. He also played a key role in convening the Working Group M12 for Biological Evaluation of Medical Devices. He has published numerous papers and is a frequent invited speaker at conferences.

Alicia Z. Karas, DVM, is the 2011 recipient of the Charles River Laboratories' Excellence in Refinement Award. She is noted for her expertise and dedication in enhancing the well-being of laboratory animals and in alleviating the pain and distress they may experience.

Sponsored by Charles River Laboratories, in cooperation with the Johns Hopkins Center for Alternatives to Animal Testing (CAAT), the award honors an individual who has made an outstanding contribution to the development, promotion, and/or implementation of refinement alternatives. "Refinement," one of the 3Rs of alternatives, refers to methods aimed at minimizing pain and distress for laboratory animals.

Karas, currently Assistant Professor of Clinical Sciences in anesthesia at Tufts School of Veterinary Medicine, has devoted her career to easing the life of laboratory animals. Her primary research interests include the assessment and treatment of pain or distress in laboratory animals, animal well-being, pain management, and pain medicine.

For information on the Charles River Laboratories' "Humane Care Initiative," please see: http://www.criver.com/en-US/AboutUs/HumaneCareInitiative/Pages/home.aspx

Emily McIvor, Senior Policy Adviser for Humane Society International/Europe, won the 2011 Henry Spira Award. She has worked on animal welfare issues at European Union level for many years, specializing in the use of animals in research and testing. As one of the lead animal welfare lobbyists in political negotiations of the EU Cosmetics Directive 7th Amendment, REACH regulation, and most recently, the revision of Europe's legislation for the protection of animals used for scientific purposes, McIvor has extensive experience with regulatory test issues and the development and validation of alternative, non-animal methods.

McIvor represents HSI/Europe on the stakeholder "mirror group" of the European Partnership for Alternative Approaches to Animal Testing, and on the management panel of the European Union-funded AXLR8 (pronounced "accelerate") project. On broader animal welfare issues, McIvor has contributed to discussions relating to the current and future Community Action Plans on the Protection and Welfare of Animals and has addressed the European Parliament's Animal Welfare Intergroup.

McIvor's dedicated efforts to improving animal welfare reflect the criteria presented by Peter Singer in the book *Ethics into Action: Henry Spira and the Animal Rights Movement*. Singer distills the methods Spira used over the years into "Ten Ways to Make a Difference." The selection criteria for this award are based upon these methods: See http://caat.jhsph.edu/programs/awards/spira/index.html

For additional information about CAAT's Awards Programs, see: http://caat.jhsph.edu/programs/awards/index.html

CAAT-Europe hosts workshop on scientific ways forward for replacement of systemic toxicity testing for cosmetics and chemicals

From 10-12 October, 35 experts from both sides of the Atlantic convened in Konstanz, Germany, to discuss five white papers prepared by David Basketter, Harvey Clewell, Thomas Hartung and Annamaria Rossi for the areas of sensitization, toxicokinetics, carcinogenicity, reproductive and repeated-dose toxicity. Four to five respondents per paper and an extensive discussion with all participants led to agreement on all papers. They are currently being prepared for publication

in ALTEX 1/2012. The papers set priorities for test/model optimization, validation, integrated testing strategies and the link to Toxicology in the 21st Century with its pathway-based approaches. A two-day event to present and discuss these papers will take place in Brussels in March 2012 (contact: Mardas Daneshian, caat-eu@uni-konstanz.de). This will be jointly hosted by a number of stakeholder organizations including ASCCT, CAAT, COACH/SEURAT-1, DZF, ecopa, ESTIV, HSI, IIVS, IVTIP, ToxCast – other organizations are in the process of deciding on co-hosting the event. It is hoped that this priority setting will help define future programs for replacement options for these complex endpoints.

Further CAAT and CAAT-Europe activities

Promotion of the 3Rs involves policy issues as well as scientific concerns. Dr Paul Locke, an environmental health scientist and attorney responsible for CAAT's policy program, and his team regularly visit Capitol Hill to discuss policy issues associated with humane science and alternatives. Much of the discussion about chemical regulation under the Toxic Substances Control Act (TSCA) focuses on the goal of protecting human health, but Locke led a Capitol Hill briefing in October, along with Rep. Jim Moran (D-VA), co-chair of the Congressional Animal Protection Caucus, to draw attention to the need for alternatives to animal testing.

"More must be done to require agencies including US EPA, the National Institutes of Health and the Food and Drug Administration along with the chemical industry to end animal testing," Locke said.

Locke recently gave a presentation at the Animal Law Conference in Portland, Oregon entitled "Humane Science: Is the End of Animal Testing Within Reach?"

See: http://altweb.jhsph.edu/news/current/animaltoxics.html

CAAT Europe and the Transatlantic Think Tank for Toxicology (t^4) hosted a workshop on developmental neurotoxicity testing with the goal of defining pathway-based and mechanism-related compounds relevant for developmental neurotoxicity (DNT) on October 4-6, 2011 in Konstanz. The experts from areas of pharmacology, toxicology, biology and alternatives to animal experiments discussed the identification of mechanistically defined compounds to map pathways for DNT and the classification of established DNT compounds according to expected *in vitro* effects and mechanisms. The results of the workshop will be published in the near future.

CAAT Europe hosted its second Information Day, this time on the topic "Status and Future of Systemic Toxicity Testing for Chemicals and Cosmetics" on October 13, 2011 in Konstanz. Speakers from academia, industry and animal welfare organizations focused on the scientific state of the art, challenges and opportunities for testing complex toxicological hazards without animals. This reflects the ongoing development of new strategies for chemicals and cosmetic ingredients safety testing in Europe and the US.

CAAT had a booth at the recent meeting of the American Association of Laboratory Animal Science (AALAS) in San Diego, California. The meeting drew 5,000 participants in the laboratory animal field. We had the opportunity to talk with many people about the 3Rs and to offer them copies of ALTEX and our new CAAT brochure.

Upcoming CAAT events

CAAT-US Information Day
Food Information Day
November 15, 2011
Baltimore MD, USA
http://caat.jhsph.edu/programs/workshops/foodinformation.html
For program and registration, contact:
Marilyn Principe (mprincip@jhsph.edu)

Evidence-based Toxicology Workshop
January 24-25, 2012
EPA, Research Triangle Park, USA
For further information contact:
mprincip@jhsph.edu

Workshop: Stakeholders Meeting re Cosmetic Review
March, Brussels, Belgium (TBA)

For up-to-date listings and information about CAAT programs and events: http://caat.jhsph.edu/programs

Recent Publications

Christiansen, S. H., Selige, J., Dunkern, T., et al. (2011). Combined anti-inflammatory effects of β(2)-adrenergic agonists and PDE4 inhibitors on astrocytes by upregulation of intracellular cAMP. *Neurochem. Int. 59*, 837-846. doi:10.1016/j.neuint.2011.08.012. PubMed PMID: 21871511.

Mattsson, C. L., Csikasz, R. I., Chernogubova, E., et al. (2011). β1-Adrenergic receptors increase UCP1 in human MADS brown adipocytes and rescue cold-acclimated β3-adrenergic receptor KO mice via nonshivering thermogenesis. *Am. J. Physiol. Endocrinol. Metab.*, 2011 Aug. 30, Epub ahead of print. doi:10.1152/ajpendo.00085.2011.

Hogberg, H. T. and Bal-Price, A. K. (2011). Domoic acid-induced neurotoxicity is mainly mediated by the AMPA/KA receptor: comparison between immature and mature primary cultures of neurons and glial cells from rat cerebellum. *J. Toxicol. 32*, 158-168.

News from ecopa

This year's ecopa General Assembly of the European Consensus-Platform for Alternatives – ecopa – was held on November 10 in the Hotel Santo Domingo in the beautiful capital city of Spain, Madrid. At the meeting the incumbent ecopa board members as well as representatives of nine national consensus platforms were present. The president of ecopa, Adela López de Cerain from REMA – the Spanish national platform – opened the General Assembly reporting on the activities on the board in the previous year, mainly focusing on the new website and the annual meeting in Milan 2010. Next, the national platform representatives presented their past year's activities. These presentations will be made available at: www.ecopa.eu

The election of the new ecopa Board was carried out as a secret ballot in compliance with the association's relevant articles. The seats for the president, for the vice president, for four national consensus platform (NCP) delegates and for three 3Rs specialists were redistributed. For the next two years Lisbeth Ehlert Knudsen, DACOPA, will serve as president of ecopa, Tuula Heinonen, FINCOPA, will be vice president, Philippe Vanparys, Belgium, is this period's treasurer, Marianne Norring, Finland, Manfred Liebsch, Germany, Erwin Roggen, Denmark, and Sophie Deleu, The Netherlands, will act as NCP delegates. Thomas Hartung, US/Germany, Troy Seidle, UK, and Marianne Kuil, The Netherlands, are the designated 3Rs experts. Directly after the election the first board meeting was held in a closed session deciding a continued effort in promoting the NCP activities, transparent communication and dissemination through this ecopa corner and the website as well as meetings and workshops organized locally, such as the REMA meeting in Madrid. Upcoming annual meetings will be held in Switzerland 2012, Germany 2013 and Norway 2014.

Ecopa is the dissemination partner in the EU 6th and 7th Framework Program projects carcinoGENOMICS, ESNATS and Sens-it-iv.

On March 15, 2011 the extension of the carcinoGENOMICS project was confirmed. As part of its dissemination strategy, the project has supported a March 27-30, 2011 scientific workshop co-organized by the British Toxicology Society and the *Nederlandse Vereniging voor Toxicologie*. A second capacity-building meeting is also envisioned. Outcome of the liver work performed in the context of the second stage of carcinoGENOMICS will be available shortly. This was a topic of discussion at the last Board meeting held in Brussels on November 16-17, 2011. A similar strategy is currently being followed for the selected kidney-based *in vitro* model. The project will end in April 2012 and it is expected that at that time two thoroughly characterized *in vitro* models for testing chemical-induced hepatic and renal carcinogenicity will be delivered. These will form the solid basis for potential follow-up projects in the area of *in vitro* carcinogenicity testing.

The Embryonic Stem cell-based Novel Alternative Testing Strategies (ESNATS) project began its 4th year in 2011. The next ESNATS annual consortium meeting will be combined with a summer school; these are planned for May 1-5, 2012 near Thessaloniki, Greece. Within the ESNATS consortium a test battery is being developed to assess different aspects of prenatal toxicity such as functional impairments and changes in the differentiation capacity after exposure to well-selected reference compounds. More specifically, a test battery, consisting of 3-4 robust test systems, covering different critical time windows of neuronal cell differentiation, is being trained with prenatal toxicants covering various toxicological mechanisms and leading to the identification of a panel of marker genes covering a wider range of prenatal toxicity.

The Sens-it-iv project officially terminated on March 31, 2011. During the last months of the project, efforts were made to establish an e-learning program supporting public access to the experimental knowledge base on assays available within the Sens-it-iv toolbox. The e-learning prototype is available online (http://www.sensitive-learning.eu). The Sens-it-iv consortium hosted a congress marking the official closure of this EU FP6-funded project on November 23-25, 2011 at the Crowne Plaza Brussels Airport Hotel with the objective of actively stimulating the transfer and implementation of knowledge acquired and of tools developed by the consortium in the areas of skin and respiratory sensitization.

SET (Germany):

The German platform, the SET Foundation, consists of representatives from industry, animal welfare, science and government. Their role is the transparent, interdisciplinary allocation of funds to eligible projects researching and implementing methods to replace and complement experiments on animals.

Following an initiative by the German Federal Ministry of Food, Agriculture and Forestry, the SET Foundation was established in 1986. The abbreviation SET stands for *Stiftung zur Förderung der Erforschung von Ersatz- und Ergänzungsmethoden zur Einschränkung von Tierversuchen* – Foundation for the promotion of alternate and complementary methods to reduce animal experiments. This approach was revolutionary, bringing together representatives from animal welfare and industry (e.g., the German Animal Protection Association, the German Federation for Animal Welfare, the German Crop Protection Association, the German Cosmetic, Toiletry, Perfumery, and Detergent Association, the Association of the German Chemical Industry and the German Trade Association of Research-based Pharmaceutical Companies) with the common goal of reducing or avoiding animal experiments.

Eligible projects aim to reduce the number of animals used and/or their distress as effectively and broadly as possible. The SET Foundation focuses its activities on the development of alternative methods, on the dissemination of information on established 3Rs methods, on the application areas of 3Rs methods and on broadening the use of 3Rs methods, for instance for training purposes.

Project funding is mainly financed by donations from industry. Since 2010 the SET Foundation receives additional support from the German Ministry of Food, Agriculture and Consumer Protection. The board of SET consists of eight members, i.e., four from the animal welfare and four from industrial associations. The chair and the deputy chair represent industry and animal welfare associations. The main duty of the board is to decide on the funding of research proposals submitted to the Foundation. Until now the SET Foundation has supported over 50 projects.

The SET Foundation is funding six ongoing projects:

– *Dr Felix Spöler, RWTH Aachen University and Prof. Dr Norbert Schrage, ACTO (Germany)*: "Development of an ex vivo dry eye model as an alternative to animal testing in pharmacological screenings". The project, which will be completed at the end of this year, is based on the Ex Vivo Eye Irritation Test (EVEIT). It uses a self-healing culture system of living corneas obtained from abattoir rabbit eyes to reduce and replace animal experiments performed during the development of new pharmaceutical products.
– *Prof. Dr Pablo Steinberg, Stiftung Tierärztliche Hochschule Hannover (Germany)*: "Development of an in vitro test system for carcinogenicity screening of chemicals with high throughput". This project uses a combination of the BALB/c-3T3 cell transformation test and the soft agar assay to detect carcinogenic properties of test chemicals. The first part of this project will be finished at the end of this year, a further year of financial support will be provided by the Doerenkamp-Zbinden-Foundation.
– *Dr Hubert Löwenheim, University of Tübingen (Germany)*: "Development of an otic stem cell based model of the inner ear: An *in vitro* model for drug development in the field of hearing loss". This project, running until September 2012, involves otic stem cells, which will be differentiated into different ear cell types. This *in vitro* model is referred to as the "mini-ear" model.
– *Dr Karin Weisser and Dr Beate Krämer, Paul Ehrlich Institute, Langen (Germany)*: "Development of an *in vitro* method for the determination of tetanus toxicity in tetanus vaccines". This project has been co-financed together with the Swiss Doerenkamp-Zbinden Foundation and the Swiss Organisation AnimalFree Research and will be completed in spring 2012. It aims to replace the current guinea pig test for the detection of active tetanus neurotoxin in vaccine production.
– *Dr Sabrina Ehnert and Prof. Dr Andreas K. Nüssler, University of Tübingen (Germany)*: "Development of a 3D flow through model for long-term culture of polarized hepatocyte-like cells *in vitro*". This project aims to develop an *in vitro* model for assessment of chronic exposure and investigation of continuous inflammation involving primary hepatocytes. It will run until early 2013.
– *Prof. Dr Gerhard Gstraunthaler, University of Innsbruck (Austria)*: "Human thrombocyte concentrates as substitutes for animal-derived serum in stem cell cultures for *in vitro* toxicity testing". The project explores the human thrombocyte lysate as a replacement for fetal bovine serum for culturing human mesenchymal and mouse embryonic stem cell culture. This project is funded until April 2013.
– *Roman Kolar, Akademie für Tierschutz, Neubiberg (Germany)*: "Analysis of EU-legislation in terms of consistency and state-of-the-art regarding the implementation of the 3Rs in the data requirements to identify potential for further improvement". This study – which has just been completed – aimed to identify remaining animal experiments in official data requirements, which by now should be replaced by accepted alternative methods.

For further information
on SET contact:
Dr Christiane Buta
Stiftung SET
Mainzer Landstraße 55
60329 Frankfurt
Germany
Phone: +49-(0)69a2556-1226
http://www.stiftung-set.de/
info@stiftung-set.de

News from NICEATM and ICCVAM

We are pleased to provide this update on recent and planned activities of the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and its Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). ICCVAM is composed of representatives from 15 U.S. Federal regulatory and research agencies that require, use, or generate toxicological and safety testing information. ICCVAM is charged by law with evaluating the usefulness and limitations of new, revised, and alternative safety testing methods with regulatory applicability and providing recommendations on their scientific validity to U.S. Federal agencies, which must respond to ICCVAM within 180 days. ICCVAM promotes the scientific validation and regulatory acceptance of safety testing methods that more accurately assess the health hazards of chemicals and products while reducing, refining (decreasing or eliminating pain and distress), and replacing animal use.

NICEATM administers ICCVAM and provides scientific and operational support for ICCVAM-related activities. Consistent with the NTP mission, NICEATM also conducts and coordinates international validation studies on high priority improved safety testing methods and strategies. NICEATM and ICCVAM collaborate to evaluate new and improved test methods and strategies applicable to the needs of U.S. Federal agencies and work to achieve national and international harmonization of safety testing methods.

ICCVAM recommends alternative method to identify chemicals and products with significant potential to cause allergic contact dermatitis

ICCVAM recently forwarded recommendations for using the murine local lymph node assay, or LLNA, to categorize the potency of some chemicals that cause allergic contact dermatitis in humans as strong sensitizers. Strong sensitizers are those substances considered to have a significant potential for causing skin hypersensitivity resulting in allergic contact dermatitis.

ICCVAM concluded that the LLNA could correctly categorize some substances as strong sensitizers using a criterion published in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). However, nearly half of the known human strong sensitizers evaluated by ICCVAM were not identified using the GHS criterion. ICCVAM concluded that additional information would need to be considered to confirm whether substances that do not meet this criterion are or are not strong sensitizers. The recommendations are based on a comprehensive test method evaluation by ICCVAM and NICEATM, and were announced July 28 in the *Federal Register*.

Substances with the potential to cause ACD can also be categorized with traditional test methods using guinea pigs. However, the LLNA uses fewer animals than guinea pig test methods, requires less time to perform, provides dose-response information, and, in most cases, eliminates the potential for pain and distress in the test animal. In accordance with the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals, the LLNA should be routinely considered when planning animal studies to evaluate whether chemicals and products are strong sensitizers in order to minimize animal use and to avoid pain and distress.

The ICCVAM report including the recommendations has been transmitted to U.S. Federal agencies for their review and response. A summary of the ICCVAM recommendations and a link to the report are available on the NICEATM-ICCVAM website at http://iccvam.niehs.nih.gov/methods/immunotox/LLNApotency.htm. Responses from Federal agencies will be available by early 2012 and will be posted on this page as they are received.

NICEATM and ICCVAM are also currently evaluating several *in vitro* and *in chemico* methods for their potential to further reduce and eventually replace animal use for ACD safety testing. Information on NICEATM and ICCVAM evaluations of methods for ACD safety testing can be found at: http://iccvam.niehs.nih.gov/methods/immunotox/immunotox.htm

ICCVAM proposes procedures to reduce animal use for eye safety testing

ICCVAM is proposing eye hazard classification criteria that will provide the same or greater level of eye hazard classification as current U.S. Federal Hazardous Substances Act (FHSA) regulations, while using 50% to 83% fewer animals. The draft recommendations are based on an analysis conducted in collaboration with NICEATM. A manuscript describing the NICEATM analysis was recently published in the journal Regulatory Toxicology and Pharmacology (Haseman et al., *Regul. Toxicol. Pharmacol. 61*, 98-104).

NICEATM announced availability of the draft recommendations and requested public comment via a *Federal Register* notice published August 12. ICCVAM will consider all public comments and comments made by its advisory committee when finalizing its recommendations. Final ICCVAM recommendations will be made available on the NICEATM-ICCVAM website and forwarded to relevant Federal agencies for their consideration.

Links to the ICCVAM draft recommendations, the *Regulatory Toxicology and Pharmacology* article, and other information about the NICEATM analysis may be found on the NICEATM-ICCVAM website at: http://iccvam.niehs.nih.gov/methods/ocutox/reducenum.htm

ICCVAM Advisory Committee meets

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) met on June 16 and 17. SACATM is composed of representatives of regulated industries and other ICCVAM stakeholders. It advises the Director of the National Institute of Environmental Health Sciences (NIEHS), ICCVAM, and NICEATM about Federally mandated ICCVAM functions and ICCVAM activities.

At the June meeting, SACATM was provided with an overview of NICEATM and ICCVAM activities and accomplishments over the past year. SACATM also received a detailed summary of the March meeting of an ICCVAM-sponsored peer review on an *in vitro* method to identify potential endocrine-active substances. In their comments following this presentation, SACATM members indicated that they felt the peer review panel conducted a comprehensive review of an impressive body of work. Summary presentations were also given on a September 2010 NICEATM-ICCVAM workshop on alternative methods for vaccine potency and safety testing, and workshops convened by NICEATM and ICCVAM in January 2011 on Best Practices for Regulatory Safety Testing. Commenters on these presentations noted that both the vaccine workshop and the Best Practices workshops had provided opportunities for productive interaction between industry representatives and regulators, and made suggestions about how future workshops could be made even more effective.

SACATM also considered nominations that had been forwarded to ICCVAM for activities supporting the further development of *in vitro* test methods for detection and quantification of botulinum neurotoxin and for detection of pyrogenic substances. SACATM endorsed further ICCVAM activity on these nominations with high priority.

Representatives from NIEHS and the National Institutes of Health provided SACATM with summaries of ongoing activities contributing to the development of alternative test methods. SACATM also received updates from representatives of international validation organizations, including the Korean Center for the Validation of Alternative Methods, Health Canada, the Japanese Center for the Validation of Alternative Methods, and the European Centre for the Validation of Alternative Methods.

Materials from the June SACATM meeting, including the agenda, background materials, public comments submitted, and all presentations, are available on the NTP website at http://ntp.niehs.nih.gov/go/8202. Minutes from the meeting will be available on this page later this fall.

NICEATM and ICCVAM convene Workshop on Rabies Vaccine Testing

NICEATM and ICCVAM convened an "International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward" on October 11-13, 2011, at the U.S. Department of Agriculture Center for Veterinary Biologics in Ames, Iowa. This workshop brought together international scientific experts from government, industry, and academia to review the available methods and approaches that reduce, refine (decrease or eliminate pain and distress), and replace animals used in human and veterinary rabies vaccine potency testing. Participants then developed an implementation strategy to achieve global acceptance and use of these alternatives.

Along with NICEATM and ICCVAM, the workshop was co-sponsored by the European Centre for the Validation of Alternative Methods, the Japanese Center for the Validation of Alternative Methods, and Health Canada. The workshop featured 17 speakers from nine countries and three breakout sessions that allowed participants to discuss the key issues to be addressed at the workshop. A poster session planned for the workshop featured presentations on current work on alternative methods that may reduce, refine, or replace the use of animals in rabies vaccine potency testing.

Rabies vaccines serve a vital role in preventing deaths from this fatal disease and controlling rabies in certain animal populations. However, determining the safety and effectiveness of rabies vaccines requires large numbers of laboratory animals and involves significant pain and distress. New methods and approaches are sought that: 1) are more humane and use fewer or no animals, 2) are faster, cheaper, and more accurate, and 3) are safer for laboratory workers. Recent scientific and technological advances may allow several alternative approaches for rabies vaccine potency testing to be implemented immediately or in the near future.

More information about the workshop is available on the NICEATM-ICCVAM website at http://iccvam.niehs.nih.gov/meetings/RabiesVaccWksp-2011/RabiesVaccWksp.htm. Presentations from the workshop and a summary of the workshop conclusions will be posted on this page. Proceedings from the workshop will be published next year in the journal Biologicals.

NICEATM presentations at Eighth World Congress available on website

Abstracts and posters presented by NICEATM staff at the Eighth World Congress on Alternatives and Animal Use in the Life Sciences are now available on the NICEATM-ICCVAM website.

At the World Congress, NICEATM staff delivered platform presentations on validation of 21st century predictive toxicology methods and validation of test methods to identify potential endocrine-active substances. NICEATM staff and ICCVAM members also presented posters that highlighted current activities and test method evaluations. Five of these presentations focused on recent ICCVAM recommendations and international regulatory acceptance for new versions and applications of the murine local lymph node assay to identify substances with the potential to cause allergic contact dermatitis. Other presentations summarized ICCVAM recommendations and regulatory acceptance of alternative methods for ocular safety testing as well as conclusions and recommendations from a NICEATM-sponsored 2010 workshop on alternative methods for vaccine potency and safety testing.

A summary of all NICEATM-ICCVAM activities, including abstracts of poster and platform presentations and copies of all posters, can be found on the NICEATM-ICCVAM website at: http://iccvam.niehs.nih.gov/meetings/8WC/8WCablst.htm

NICEATM-ICCVAM requests nominations and submissions of test methods with potential regulatory applications

NICEATM and ICCVAM welcome nominations and submissions from the public for new or revised alternative safety testing methods with the potential to improve the accuracy of safety assessments and the potential to reduce, refine, or replace the use of animals. Test methods that incorporate advances in science and technology are especially encouraged.

- *Nominations* can be submitted for proposed test method validation studies, specific test method or validation issues, or requests for test method evaluations. Such nominations are typically addressed with international validation studies, workshops, conferences, or test method independent scientific peer review meetings.
- When validation studies for a test method have been completed that adequately characterize its usefulness and limitations for a specific proposed regulatory requirement or application, a *submission* can be sent to ICCVAM for review and technical evaluation of the test method. ICCVAM then develops a test method evaluation report and formal recommendations that are forwarded to U.S. Federal agencies for acceptance consideration.

Organizations or individuals that wish to propose nominations or submissions of promising test methods are encouraged to contact NICEATM for information and guidance on preparing proposals. Submission and nomination guidelines are also available on the NICEATM-ICCVAM website at: http://iccvam.niehs.nih.gov/SuppDocs/submission.htm

For more information

Questions about NICEATM and ICCVAM activities are welcomed and can be directed to Dr. William S. Stokes, Director, NICEATM, at niceatm@niehs.nih.gov; phone +1 919 541 2384; fax +1 919 541 0947. Copies of documents mentioned in this update can also be obtained by contacting NICEATM.

Information on the availability of NICEATM and ICCVAM draft documents, requests for nominations of experts to participate at workshops and on peer review panels, and specific information about NICEATM-ICCVAM meetings are communicated via the ICCVAM-all e-mail list and in notices posted in the U.S. Federal Register.

Subscribers to the ICCVAM-all e-mail list are notified directly of NICEATM-ICCVAM activities. Subscribers receive e-mail notification of NICEATM-ICCVAM Federal Register notices, availability of NICEATM-ICCVAM reports, notices of upcoming meetings, requests for public comments or data, and other events of interest to our stakeholders. If you would like to subscribe to the ICCVAM-all list, or for more information, please visit the NICEATM-ICCVAM website at: http://iccvam.niehs.nih.gov/contact/ni_list.htm