News from the American Society for Cellular and Computational Toxicology

The ASCCT is pleased to announce it is now accepting abstracts for its 2nd Annual Meeting, *The Future is Here: Practical Application of Emerging Scientific Tools*, which will be held on October 31, 2013 on the NIH Campus in Bethesda, MD, outside Washington, DC. Specific details can be found on the website: http://www.ascctox.org

The planning committee will select four abstracts for oral presentations during the afternoon of this 1-day meeting. The remaining submitters will be invited to present posters of their research or policy analyses during a dedicated poster session. Abstracts are due August 31.

In the morning, attendees will enjoy plenary presentations by Donald Ingber from Harvard University's Wyss Institute for Biologically Inspired Engineering and Thomas Knudsen from the Environmental Protection Agency's National Center for Computational Toxicology. Dr Ingber will present progress with "human-on-a-chip" models developed for toxicity testing and disease research. Dr Knudsen will present the virtual embryo research project "vEmbryo," which aims to develop new tools for developmental toxicity assessment of chemicals.

The two plenaries will be followed by a multi-stakeholder panel discussion. Steven Bradbury, Director of the Office of Pesticide Programs at EPA and Suzanne Fitzpatrick, Senior Scientist at the Food and Drug Administration will be joined by experts from industry and NGOs. The aim of the panel is to discuss the application of ground-breaking tools, such as those described in the plenary sessions, to current and future regulatory programs, and the challenges and opportunities inherent within this paradigm shift.

The day will be capped off by an ASCCT-member business meeting and a cocktail party.

On behalf of the ASCCT Board of Directors, we hope to see you there.

Kristie Sullivan
Secretary, ASCCT
http://www.ascctox.org

CAAT*feed*

High Content Imaging Technology in safety sciences: probing cell function, workshop, and public Information Day in October 2013 in Mainz, Germany

This information day on October 24, 2013 jointly organized with ECOPA, ESTIV, IVTIP, and SET, will focus on the possibilities of the HCI technology for examination of damage mechanisms and toxic effects of chemicals. Probes for organelle and cell function and reporter systems for organ and systemic toxicity will be presented. The discussion will address questions on how phenotypic and signaling changes are linked to functional impairment and cell fate. Furthermore, the implementation of the HCI approach in (regulatory) safety sciences, latest technical advances and perspectives from the fields of systems biology/toxicology will be important topics during this event.

The information day will be preceded by a workshop (by invitation only).

For information: Mardas.Daneshian@uni-konstanz.de

Recordings now available from CAAT co-sponsored workshop: Lessons Learned, Challenges, and Opportunities: The US Endocrine Disruptor Screening Program

The CAAT co-sponsored workshop was held on April 23-24, 2013 in Research Triangle Park, North Carolina.

This open workshop was designed to focus on the science and experience to date and was not intended to be a forum to discuss individual chemicals and their performance in the Tier 1 screening assays. Lessons learned and the discussion/outcomes of this workshop will support the use and implementation of the proposed advancements described in the EDSP21 (Endocrine Disruptor Screening Program – 21st Century) and TT21C (Toxicity Testing in the 21st Century) visions. The workshop report is in preparation.

For more information see the workshop's webpage: http://altweb.jhsph.edu/news/2012/EDSP_recordings.html

Recordings now available from the Scientific Roadmap for the Future of Animal Free Systemic Toxicity Testing

Workshop Recordings of presentations are now available from the Scientific Roadmap for the Future of Animal Free Systemic Toxicity Testing workshop. The meeting was held May 30-31, 2013 at the FDA building in College Park, Maryland. It was attended by 120 people in person and 65 webinar participants. Extensive discussions led to a broad endorsement of the roadmap (Basketter et al., ALTEX, 2012). The workshop report is in preparation.

For more information on the workshop, please see the workshop's webpage: http://altweb.jhsph.edu/news/2012/roadmap_recordings.html

EBTC Session at International Congress of Toxicology, June 30-July 4, 2013, Seoul, Korea

The Congress was held June 30-July 4, 2013 in Seoul, South Korea (see http://www.ict2013seoul.org) and included a session on "The Evidence-Based Toxicology Collaboration." The session featured presentations on the need for evidence-based approaches in toxicology (Ian Kimber, University of Manchester), activities of the Evidence-Based Toxicology Collaboration (EBTC) (Thomas Hartung, Johns Hopkins University), methodologies and methods of EBT (Sebastian Hoffmann, seh consulting), and EBT as a toolbox for the assessment of tests and testing strategies (Thomas Hartung on behalf of Richard Judson, US Environmental Protection Agency). The speakers are members of the North American or European steering committees of the EBT Collaboration. CAAT serves as the secretariat of the EBT Collaboration, which promotes the use of evidence-based approaches to strengthen decision-making in safety sciences (see http://www.ebtox.com).

CAAT cosponsored FDA/NIEHS/NCATS/IQ workshop on May 10, 2013: Developing Microphysiological Systems for Use as Regulatory Tools – Challenges and Opportunities

CAAT Director Thomas Hartung chaired a session on "Inventing Microphysiological Systems: Cell Types, Tissues, and How to Apply Them" and spoke on good cell cultures and quality control. CAAT has from the beginning been part of the discussion around new tools for the assessment of countermeasures for biological and chemical warfare and terrorism. The workshop's goal was to provide a forum for academia, industry, and regulatory agencies to address two objectives: 1) discuss essential elements needed to develop microphysiological systems as regulatory tools, and 2) discuss pathways to qualification as regulatory tools.

t4 workshop: Adversity vs adaptation: determining the most appropriate point-of-departure based on *in vitro* toxicity data

A workshop was organized in the Netherlands by Dr Bas Blaauboer on June 12-14, 2013 bringing together a group of experts from areas of *in vitro* toxicology, systems biology, pathophysiology, and structure-activity relationships to discuss this matter and develop recommendations. The use of cell cultures in toxicity testing of chemicals has the potential to provide a detailed picture of the changes of many parameters at once. Even if these changes show a clear concentration/effect relationship, care must be taken in interpreting the results in view of their relevance to the compound's toxicity. Most likely, the sensitivity of these detailed studies will be much higher than what can be derived from the interpretation of apical endpoints in an animal study, e.g., due to the lack of compensatory/homeostatic processes, usually working *in vivo*. The question is then: when is a change related to an adverse effect, and when should a change be interpreted as falling within the boundary of the physiologically "normal" adaptive or homeostatic range? The report is in preparation.

t4 workshop July 8-10, 2013 in Ispra, Italy, on ITS for Safety Assessment using skin sensitization as example

To further shape the concepts for Integrated Testing Strategies this workshop is coorganized with BASF, IFRA, RIFM, and ESTIV. It is now well recognized that the future of chemical risk assessment will be through a combination of tests (*in vitro, in silico, in vivo*) that can clarify the Mechanism (Mode of Action) and cover different applicability domains. In spite of this shared awareness, the way toward this goal is still unclear as there are controversies starting from the definition of an ITS, how it can be validated and last, but not least, there are no informatics tools that can be used for this purpose. One of the main challenges is to accommodate the flexibility ITS require, e.g., to respond to varying levels of uncertainty or resolution needed, with the requirement of standardization that is mandatory for regulatory applications. The aim of this workshop is to layout a basis for the construction of transparent, objective, and consistent ITS tools that fulfill the needs of risk assessors. It uses the example of skin sensitization, where such integration of the assays recently evaluated and validated is imminent and the mechanistic understanding is advanced. Questions to be addressed: Do we need to start with guideline tests for a tiered strategy? Which *in vitro* and *in silico* methods can be utilized? Are there other endpoints that are as advanced as skin sensitization? How do we assess relevance to humans of ITS? Which statistical and/or mathematical tools are available for relevant integration of data from different sources? Do we need a new dedicated system? How should we assess the predictive performance of ITS? Participation in the workshops is by invitation only.

CAAT-Europe and the 'European Refinement Initiative': Symposium on 'Science-based Refinement'

The Center for Alternatives to Animal Testing-Europe (CAAT-Europe), F. Hoffmann-La Roche AG, and Novartis International AG invite you to the Symposium 'Science-based Refinement' in the frame of the 'European Refinement Initiative'. Representatives from pharmaceutical and chemical companies, contract research organizations, animal breeders and regulatory bodies will present their perspectives regarding animal welfare indicators, experimental design, and refinement in regulatory studies *inter alia*. This two-day meeting will take place on September 3, 2013 at the facilities of F. Hoffmann-La Roche AG and on September 4, 2013 at the facilities of Novartis International AG, both in Basel, Switzerland.

CAAT receives $ 250,000 NIH sub-grant for pyrogen test

The pyrogen test, developed by CAAT director Thomas Hartung, was adapted over the last few years to airborne pyrogens, a possible risk factor for various lung diseases. As an extension to an NIEHS grant to Dr Nadia Hansel (PI) in the School of Medicine (#3R01ES018845-04S1) Genetic Susceptibility to Asthma and Indoor Air Pollution in Peru, Thomas Hartung as project leader now received a sub-grant (May 2013 - April 2015) to apply this technology.

CAAT postdoc researcher David Pamies receives James G. Wilson Presentation Award

CAAT's David Pamies won the James G. Wilson Presentation Award at the 2013 Teratology Society meeting in Tucson, Arizona for his talk on "A neurodevelopmental human *in vitro* 3D model for the assessment of gene/environment interactions." This award was established in honor of James G. Wilson, one of the founding members of the Teratology Society, and recognizes the work of students and

postdoctoral fellows in the field of teratology. It is awarded based on the content and quality of the oral presentations.

CAAT-Europe junior scientist Anne Krug receives David Ray award at 4th International Neurotoxicology Association meeting

The conference Neurodevelopmental Basis of Health and Disease was held June 9-13, 2013 in Egmond aan Zee, The Netherlands (www.INA14.org). CAAT contributed presentations and posters by Drs. Marcel Leist, Helena Hogberg, Lena Smirnova, and Anne Krug, who won the David Ray award. The award was established in honor of David Ray, one of the founding members of the Neurotoxicology Association and recognizes the work of students and postdoctoral fellows in the field of neurotoxicology. It is awarded based on the content and quality of the oral presentations.

BBC article: "Will We Ever... Eliminate Animal Experimentation?" featuring Thomas Hartung

http://altweb.jhsph.edu/news/2012/bbc_article.html

Job opening: Post-Doctoral Researcher (Humane Toxome Project)

http://altweb.jhsph.edu/news/2012/job_opening_htp.html

Upcoming Events

Symposium on Social Housing of Laboratory Animals
August 22-23, 2013
NIH Natcher Center, Bethesda MD
http://caat.jhsph.edu/programs/workshops/social_housing.html

Call for Proposals – CAAT Science-based Refinement Awards (2014 grant period)
Deadline: September 30, 2013
http://altweb.jhsph.edu/news/2012/AWE_call_for_proposals_2014.html

Planned one-day event on Evidence-based Food Toxicology
Fall 2013 (date t.b.d.)
Teaming up with FDA CFSAN / USDA / EPA ToxCast / GMA / PEW / ILSI we plan to discuss the PEW data gap analysis for food additive safety, the ToxCast phase 2 data release (Sep 2013) including the analysis for food-related substances CAAT currently performs with CFSAN, Tox-21 approaches to safety sciences and data integration, challenges and opportunities for industry and risk communication as well as for regulation, the Evidence-based Toxicology Collaboration, translating Evidence-based Medicine to Toxicology, and Evidence-based regulatory science emerging internationally. A date at the auditorium of Johns Hopkins SAIS in Washington is currently being secured.
For information: Marilyn Principe (mprincip@jhsph.edu)

Green Toxicology Information Day
November 22, 2013, Baltimore
CAAT last year teamed up with EPA (Nick Anastas) to jointly organize the Toxicology and Sustainable Molecular Design Conference at University of Connecticut, December 11, 2012 (http://www.epa.gov/region1/tsmd/). This will be continued with a similar event in Baltimore in November 2013. We plan to create a task force on Green Toxicology to steer further activities.

Fourth International Conference on Alternatives for Developmental Neurotoxicity Testing (DNT)
May 12-14, 2014 Philadelphia, PA
Call for Abstracts – Deadline: December 31, 2013
http://altweb.jhsph.edu/news/2012/dnt4_call_for_abstracts.html

t⁴ workshop with Agilent
November 11-12, Baltimore
Application of Metabolomics in Toxicology Research
(by invitation only)

Public Information Day on Toxicometabolomics
November 13, Baltimore

t⁴ workshop with BASF
November 11-12, Baltimore
Quality assurance of emerging technologies in toxicology – Metabolomics
(by invitation only)

In Vitro Medical Devices Testing Symposium
December 10-11, 2013
Mt. Washington Conference Center, Baltimore MD
http://altweb.jhsph.edu/news/2012/med_device_symp.html

9th World Congress on Alternatives and Animal Use in the Life Sciences
Humane Science in the 21st Century
August 24-28, 2014
Prague, Czech Republic
http://www.wc9Prague
Please download and share the PDF (http://altweb.jhsph.edu/news/2012/WC9_Flyer_web.pdf), which contains full details about next year's World Congress.

Recent Publications

Bouhifd, M., Hartung, T., Hogberg, H. T., et al. (2013). Review: Toxicometabolomics. *J Appl Toxicol*, Epub ahead of print. doi 10.1002/jat.2874

Krug, A. K., Balmer, N. V., Matt, F., et al. (2013). Evaluation of a human neurite growth assay as specific screen for developmental neurotoxicants. *Arch Toxicol*, Epub ahead of print.

Leist, M., Hartung, T. (2013). Inflammatory findings on species extrapolations: humans are definitely no 70-kg mice. *Arch Toxicol 87*, 563-7.

Ramirez, T., Daneshian, M., and Kamp, H. (2013). Metabolomics in toxicology and preclinical research. *ALTEX 30*, 209-225.

van Vliet, E., Eixarch, E., Illa, M., et al. (2013). Metabolomics reveals metabolic alterations by intrauterine growth restriction in the fetal rabbit brain. *PLoS ONE 8*, e64545.

ecopa

Implementation of Directive 2010/63/EU

Directive 2010/63/EU on the protection of animals used for scientific research, adopted on 22 September 2010 came into force on 1 January 2013 across Europe, i.e. all Member States had to have translated the Directive into national legislation by 10 November 2012 (§ 61, 2010/63/EU), ensuring the application of its provisions as of 1 January 2013. At the moment there are notifications regarding the transposition of Directive 2010/63/EU from Austria, Bulgaria, Czech Republic, Denmark, Estonia, France, Ireland, Latvia, Lithuania, Luxemburg, Slovakia, Spain, Sweden, and the United Kingdom. The notifications regarding the full transposition of the Directive are still awaited from Belgium, Cyprus, Finland, Germany, Greece, Hungary, Italy, Malta, The Netherlands, Poland, Portugal, Romania, and Slovenia.

The European Commission has already initiated infringement procedures against two Member States due to non-compliance with the transposition deadline: against Hungary on 30 May – its notified transposition was found incomplete – and against Malta on 20 June. It is expected that the European Commission will initiate infringement procedures against other Member States that did not comply with the deadline and against Member States with incomplete translation of the Directive into the national legislation. Decisions on legal consequences of the infringement are expected shortly, as these are thought to provide the necessary incentive for implementation of the Directive on a national level.

Mardas Daneshian

norecopa

Norecopa: Norwegian Consensus Platform for Alternatives to Animal Experimentation

Resources available from an International Consensus Meeting on Agricultural Animals

Norecopa, the Norwegian consensus-platform for the 3Rs, arranges international consensus meetings on specific areas of research involving animals. The latest meeting was held in September 2012 entitled *Harmonisation of the Care and Use of Agricultural Animals in Research*.

All the presentations from this meeting and a compilation of relevant guidelines are now available for download from the meeting's website (http://www.norecopa.no/sider/tekst.asp?side=182). The site also contains a 12-page consensus document describing the participants' views of tasks that should be carried out to increase implementation of the 3Rs in this area. Among other topics, the meeting addressed the consequences of the new EU Directive and described the new edition of the US FASS *Guide for the Care and Use of Agricultural Animals in Research and Teaching*. Norecopa hopes that the resources on this website may be useful for the continuing professional development of all those involved in the use of farm animals in research. Norecopa started an e-mail discussion forum after the meeting for those interested in this subject. This forum is open to people who were not at the meeting following nomination by one of the participants.

Norecopa has also arranged international consensus meetings on the care and use of wildlife and fish in research, from which all presentations are available on the internet (http://www.norecopa.no/sider/tekst.asp?side=21).

For more information, please contact Adrian Smith (adrian.smith@vetinst.no).

Nordic animal welfare organization sponsors the further development of the NORINA database

The NORINA database contains information on nearly 4,000 products that may be used as alternatives or supplements to animals or animal material in teaching and training, at all levels from junior school to university. The database is available free on the internet (http://oslovet.norecopa.no/NORINA) and was developed by Karina Smith (karina.smith@vetinst.no). Norecopa has received funding from the Nordic Society against Painful Experiments on Animals for 3 years so that Karina may continue the work of updating and enlarging this database. She also manages TextBase (http://oslovet.norecopa.no/textbase), which contains information on over 1,500 books of relevance to laboratory animal science and the 3Rs.

Implementation of Directive 2010/63/EU

Norway is not part of the EU, but as a member of the European Economic Area (EEA) it is in the process of writing new legislation that will implement the Directive in the course of 2013. At the same time, the system for approving and monitoring animal experiments in Norway is being radically changed, so this will be a challenging year for the laboratory animal community. Norecopa is collaborating closely with the Norwegian authorities and animal facilities in this matter.

Norecopa's 3R prize and annual seminar

Norecopa awards an annual prize of NOK 30,000 (approx. € 4,000) to individuals or groups who have made significant contributions to the development or implementation of 3R-alternatives. This prize is awarded during Norecopa's annual seminar, which in 2013 was held in Oslo on June 3. This year's prize was awarded to Dr Goril Eide Flaten, who has developed a model membrane (PVPA: phospholipid vesicle-based permeation assay) for simulating the passage of molecules over a membrane, to replace *in vivo* work on, in particular, chemicals that cross the skin and intestines.

News from NICEATM and ICCVAM

ICCVAM Committee responds to NIEHS Director's statement on the future of NICEATM and ICCVAM

ICCVAM has responded to a recent editorial by National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP) Director Linda Birnbaum that addressed the current status and future direction of ICCVAM.

In the editorial, published in the Feb. 1 issue of *Environmental Health Perspectives*, Dr Birnbaum presented a new vision for NICEATM and how NICEATM will interact with ICCVAM in the future. The goals of the new vision are to allow ICCVAM's activities to be driven by the regulatory agencies that participate on ICCVAM and to enable NICEATM to support ICCVAM more effectively in addressing how data from high-throughput assays can be integrated into the regulatory framework.

In a letter released after its April meeting, ICCVAM states that the committee is "pleased to see the new philosophy for ICCVAM" and that it looks forward to "working with NICEATM to forge the new direction" described in the editorial. The committee expects that the proposed changes will improve efficiency of the ICCVAM test method review process and its relevance to the agencies.

Links to Dr Birnbaum's editorial and the ICCVAM response are available on the ICCVAM website at: http://iccvam.niehs.nih.gov/announcements/ICCVAM-all/2013-02-06-EHP.htm

ICCVAM stakeholders will have an opportunity to learn more about and comment on the direction and scope of future activities at the upcoming meeting of ICCVAM's advisory committee. The Scientific Advisory Committee on Alternative Toxicological Methods will meet at NIEHS on September 24, 2013. Information about the meeting is available on the NTP website at: http://ntp.niehs.nih.gov/go/32822. The meeting will be webcast, and a link to the webcast will be available on this page on the meeting days.

Acting NICEATM Director presents at Workshop on Stem Cells in Cardiotoxicity

Cardiovascular disease is the top cause of death in the United States, and drug and chemical exposure can be a factor in cardiovascular disease. The use of cultured heart cells, or cardiomyocytes, derived from stem cells holds promise for research to understand how chemicals can affect heart muscle function.

Acting NICEATM Director Warren Casey, Ph.D., presented at a workshop in March that assessed the current status and potential applications of the use of stem cell-derived cardiomyocytes for studying

cardiotoxicity. Casey joined an international group of presenters representing research institutions, pharmaceutical companies, and government agencies at a workshop on "Stem Cell-Derived Cardiomyocytes as Models of Cardiac Pathobiology and Toxicology," sponsored by the Health and Environmental Sciences Institute (HESI).

The goal of the workshop was to evaluate how such technologies may be used to evaluate risks to human cardiac health presented by pharmaceuticals and environmental chemicals. Topics discussed included the biology of cultured cardiomyocytes, specific approaches to using them to assess toxicity, how those approaches might be used to benefit public health, and future research and development needed to achieve those public health benefits.

Casey's presentation described how testing approaches that use cultured cells might be used in regulatory or safety decision-making contexts. The use of stem cells and other technologies can provide information about the mechanisms underlying toxicity and disease, and may be particularly helpful in better understanding the role that human genetic diversity plays in susceptibility to toxicity. However, as emerging technologies are developed for safety testing, appropriate validation criteria need to be developed so that the data provided by these technologies are useful to regulators.

A report from the workshop will be published in the scientific literature, and the recommendations will help pharmaceutical companies and other stakeholders develop improved approaches for this important safety testing area.

Workshop on Alternative Models and Biomarkers for Cardiotoxicity planned for October

The role of chemical exposure in cardiovascular disease will be further considered at an upcoming workshop entitled "Translational Alternative Models and Biomarkers Predictive of Drug or Chemical Cardiovascular Risk." Participants in the workshop will assess the state of the science for toxicity testing for cardiovascular risk assessment and discuss how to develop translational models to advance assessment and predictivity of cardiovascular risk from drug and chemical exposures. The workshop is being organized by NICEATM along with HESI, the U.S. Environmental Protection Agency, and GlaxoSmithKline.

Cardiovascular safety is a focus of keen interest for clinical researchers, environmental health researchers, government regulators, and drug developers. Testing methods are highly variable across regulated industries, with robust requirements for pharmaceutical testing but no requirements for industrial chemicals despite potential risks for occupational, environmental, and public exposures. Cardiovascular safety testing methods using animals currently focus on gross organ pathology, histopathology and the evaluation of serum markers, and do not adequately predict chronic risks.

This workshop will provide an opportunity for scientists involved in safety assessment of drugs and chemicals to work together towards development of alternative methods and models for cardiovascular safety and health risk assessments. Participants will review the status of regulatory testing for cardiovascular safety, identify the information gaps that prevent adequate risk assessments and safety assessments, and identify and prioritize future research initiatives using a variety of testing approaches that could address those information gaps.

The workshop will be held October 10-11, 2013, at NIEHS in Research Triangle Park, North Carolina. An agenda for the workshop, registration information, and additional information will be available soon on the NIEHS and ICCVAM websites.

U.S. Consumer Product Safety Commission Issues Guidance on Assessment of Sensitizing Substances

The U.S. Consumer Product Safety Commission (CPSC), an ICCVAM member agency, has announced new guidance to clarify the definition of "strong sensitizer" as the term applies to substances and products regulated by the CPSC. The CPSC also issued a proposal to update the supplemental definition of "strong sensitizer" under the Federal Hazardous Substances Act (FHSA).

The CPSC guidance document is titled "Strong Sensitizer Guidance." Issued in March, it is meant to assist manufacturers of chemical products in understanding how the CPSC assesses whether such products might be strong sensitizers and thus require cautionary labeling under the FHSA. The document describes the types of data that the CPSC considers in making such a determination and available methods for generating such data. It notes that a determination that a particular product is a strong sensitizer must occur on a case-by-case basis and does not solely depend upon the presence of a strong sensitizer in the product.

The guidance document is available on the CPSC website at: http://www.cpsc.gov/Global/Regulations-Laws-and-Standards/Regulated-Products-Rules/strongsensitizerguidance.pdf

The CPSC proposal to update the definition of "strong sensitizer" under the FHSA would update the definitions for "sensitizer," "significant potential for causing hypersensitivity," "normal living tissue," and "severity of reaction." The goals of the updated definitions are to "eliminate redundancy, remove certain subjective factors, incorporate new and anticipated technology, rank the criteria for classification of strong sensitizers in order of importance, define criteria for 'severity of reaction,' and indicate that a weight-of-evidence approach will be used to determine the strength of the sensitizer." The CPSC will consider public comments received on the proposal as it develops the final update to the FHSA, which will be announced in the *Federal Register*.

IIVS News & Views

Industry Council Formed to Advance Regulatory Acceptance of Non-Animal Testing Methods

IIVS announces the formation of ICARAA: Industry Council for the Advancement of Regulatory Acceptance of Alternatives. ICARAA was formed in response to international regulations that still require animal testing to assess the safety of cosmetic and personal care products. "Many companies have been working for decades to eliminate animal testing," states Dr Rodger Curren, President of IIVS. "As a non-profit organization with a mission to expand the use and acceptance of *in vitro* methods, IIVS is well positioned to assist international regulatory agencies in the adoption of such technologies. With the combined support of the industry partners we are able to significantly expand and sharpen our efforts."

ICARAA activities focus on educational programs that include lectures, laboratory demonstrations, hands-on training and data interpretation. Priority is given to those *in vitro* tests that have been widely used by the personal care and cosmetic industries and recognized by the OECD. Currently, ICARAA is also working with a major university and a biotechnology company to help increase the number of *in vitro* testing laboratories in China as well as assist with the development of the technology required to conduct *in vitro* testing. ICARAA's overall goal is to facilitate movement away from animal testing by China's regulatory agencies.

ICARAA is currently comprised of a number of companies including: Avon Products, BASF SE, British American Tobacco Group Research & Development, Colgate-Palmolive Company, The Estee Lauder Companies, Inc., Kimberly-Clark Corporation, Mary Kay Inc., and Unilever.

Workshop Report – Inhalation Toxicity: Pathways to Better Methods

IIVS, the Physicians Committee for Responsible Medicine (PCRM), and the Alternatives Research and Development Foundation (ARDF) co-sponsored a workshop held May 1-3 in Gaithersburg, Maryland focusing on surveying promising alternative methods to identify toxic events in the respiratory system caused by inhaled agents. Models that can mimic the anatomy and physiology of the human respiratory system and its responses to chemical exposures are relied on to determine this type of toxic response. Current animal models used for regulatory purposes provide practical, ethical, and scientific challenges; therefore, toxicologists are developing *in vitro* and *in silico* approaches. However, no single approach or combination of approaches used in screening or hazard identification has been accepted by regulatory agencies.

One difficulty in establishing the scientific credibility of *in vitro* and *in silico* approaches has been the ability to clearly describe why the non-animal approaches are relevant to the *in vivo* response. Recently the OECD has tried to address this issue by developing the concept of Adverse Outcome Pathways (AOPs). This approach relies on identifying individual "key" molecular, cellular, and organ-specific events which lead to known apical toxicity effects. Developing *in vitro* or *in silico* assays which address the individual events in an AOP makes it easier to develop a comprehensive non-animal testing strategy whose scientific relevance can be more easily understood.

The May Inhalation Toxicity Workshop focused on determining key AOPs for inhalation toxicity and identifying gaps in knowledge in this area that should be addressed with additional research. Attendees included experts in respiratory toxicology, model development, and exposure systems who represented broad segments of industry, research institutions, academia, and government.

The first day consisted of lectures considering how the (mostly) *in vivo* data generated to fulfill safety assessment and/or regulatory needs in the chemical, pharmaceutical, personal care, and environmental health sectors are used. Participants explored methods used to model and measure the dosimetry of compounds in various sections of the respiratory system. Lectures providing overviews of the most promising *in vitro* models of the respiratory tract – from monolayer to coculture and three dimensional systems – finished out the day.

Attendees examined computational approaches, which can be used to sort, group, or prioritize many substances;

place single substances into a hazard or risk assessment context; or provide evidence to delineate AOPs on the second day. The day concluded with lectures on how AOPs can be used as an overarching framework to organize chemical effect and biological pathway knowledge in order to identify key pieces of molecular information necessary to predict apical effects without *in vivo* testing.

The group formed breakout sessions on the last day to address common themes uncovered through the given lectures. Areas of interest identified by the attendees which deserved further attention were: issues of dosimetry, delineating an AOP for respiratory sensitization, and general recommendations such as standardizing the quality of *in vitro* data presented in peer reviewed journals. The breakout groups will continue to work collaboratively over the coming months to more fully develop their recommendations, which will subsequently be published. Participants plan to submit a proposal to develop an AOP for respiratory sensitization to the OECD in early summer. If added to the OECD work plan, the AOP will be developed collaboratively over the coming months.

Cruelty Free International (CFI) Supports IIVS to Introduce Alternative Testing Methods to Vietnam

Vietnam is part of the ASEAN organization (Association of South East Asian Nations) but still requires animal testing for cosmetics in certain circumstances. Cruelty Free International (CFI) has provided funding to IIVS to provide training in Vietnam on the topic of non-animal safety testing methods used for cosmetics.

IIVS staff has visited Vietnam to speak with scientists, tour laboratory facilities, and discuss the feasibility of conducting a hands-on and lecture training for select alternative methods. The support from CFI will be used as part of IIVS' International Outreach Program (IOP) which facilitates information exchange and actively addresses regulatory policy in countries where animal testing is still required. IIVS' IOP provides guidance, assistance, and training to government agencies, domestic and international companies, and other interested parties seeking to implement and support non-animal testing methods.

To read more about IIVS International Outreach or other programs, please visit our website at: http://www.iivs.org