



## News

# EU: EU plans to delay ban of animal experiments for cosmetics

The EU plans to indefinitely postpone the final ban on the sale of cosmetics containing compounds tested on animals, which is scheduled for the 11<sup>th</sup> of March 2013, because insufficient animal-free test methods are available. The Society Doctors Against Animal Research Germany accuses the EU Commission of not considering all animal free options and demands that the date be held.

Since 2004 the 7<sup>th</sup> Amendment of the EU Cosmetics Directive bans animal experiments for cosmetic end products and since 2009 it also bans the EU-wide sale of cosmetic ingredients and end products tested in animals, independent of whether animal-free methods are available. The only exceptions are three animal experiments: chronic toxicity, reproductive toxicity and pharmacokinetic experiments. These three tests are scheduled to be banned on the 11<sup>th</sup> March 2013 according to the Cosmetics Directive.

The EU Commission now plans to postpone this ban indefinitely, as a report

commissioned by the European Commission finds that insufficient validated animal-free tests will be available by 2013. In addition, two further animal experiments to test for allergic and cancer potential, which were banned in 2009, shall be reinstated.

Doctors Against Animal Experiments together with the European Coalition to End Animal Experiments (ECEAE) are currently working on a detailed response, which shall be submitted on occasion of a public hearing of the European Commission. The response will show that many animal-free methods that are far advanced in their development were not sufficiently considered in the report. For example, a test system for long-term testing of toxic effects on human lung tissue is sold by a specialised company. The method has already been evaluated in a series of studies to determine its relevance and predictivity. The report however states that well-studied long-term test methods will not be available in fewer than ten years.

Doctors Against Animal Experiments Germany demands that the planned ban date not be postponed. "This is neither ethically nor scientifically justifiable and sends industry the entirely wrong signal," says Wolfgang Stengel, M.D, specialist for pharmacology and toxicology at Doctors Against Animal Experiments Germany. The past has shown that a legal ban can successfully stimulate the development of animal-free systems. "The current state of knowledge and the currently available animal-free test methods based on human cells or computer modelling allow the use of a wide spectrum of products without safety concerns", he explains. Further, many thousands of ingredients for cosmetic products have already been in use for many years.

Doctors Against Animal Experiments  
Press release of 8<sup>th</sup> October 2010  
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# EU: Research animal use holds steady

According to the latest statistics published by the European Commission, about 12 million animals were used for scientific purposes in the European Union in 2008. This number is similar to that of 2005 when the last statistical report was published. But the figures mask the impact of the gradual introduction of alternatives for safety testing of chemicals and drugs that use far fewer animals. And they have not yet been affected by the deluge of animal tests that stand to be carried over the next decade or more as a result of the REACH (Registration,

Evaluation, Authorisation and Restriction of Chemicals) legislation, which requires safety testing of all chemicals marketed in the EU by 2018.

The largest proportion of research animals is used in fundamental biology studies, and this has increased from 33% in 2005 to 38% in 2008 – an increase of more than half a million animals. Most of this rise is attributable to the growing use of transgenic mice. The total number of mice used for all scientific purposes increased by more than 690,000 in this period. The number of animals used in

research and development for human and veterinary medicine dropped from 31% to around 23% over the same period.

More than two-thirds of the animals are used by just five of the EU's 27 member states – France (19.4%), the United Kingdom (18.9%), Germany (16.9%), Spain (7.5%) and Italy (7.2%) – where much of the EU's pharmaceutical industry is based.

In accordance with EU rules, no great apes were used in either 2005 or 2008. All new-world monkeys used were bred in captivity in Europe.



The proportion of animals used in toxicology tests for drugs and industrial chemicals remains the same: 8.7% of the total, representing a little over one million animals. Of these, 80,000 were used for safety testing of industrial chemicals and consumer products. In 2005, this number stood at 100,000, and in 2002 – when there were just 15 EU member states – the figure was 140,000. This steady decline is attributable to the increasing use of validated safety tests that use no, or fewer, animals. But companies meeting the requirements of the REACH legislation will add a further nine million animals by 2018, according to estimates of the European Commission.

Alternative methods of toxicity testing have already had some effect on animal use, but a bigger impact is expected in the coming years. Thanks to accepted modifications in LD<sub>50</sub> testing – which determines how much of a compound is required to kill half of the animals in a given sample – the number of rats used per chemical tested has fallen from 45 to a maximum of 12. This is reflected in a drop in the number of rats used in such tests from 19,700 in 2005 to just 7,000 in 2008. Meanwhile, new alternative methods meant that the number of rabbits used for skin irritation tests fell from 5,100 to 4,200, and rabbits used in eye irritation tests numbered 2,100, down from 4,000. The alternatives to the rabbit

pyrogen test, which were accepted by the European Pharmacopoeia this year, promise to replace tens of thousands of rabbit tests for fever-inducing activity of injectable medication a year.

But, for all the reductions, overall numbers have remained about the same, meaning that some must be on the up. One factor raising the numbers of lab mice used is BoTox, a highly toxic biological preparation of botulinum toxin that is used clinically to treat painful muscle spasm. However, it is much more widely used cosmetically to reduce wrinkles. Each batch of BoTox must be safety tested on mice: in 2005, this required 33,000 mice; by 2008 this had increased to 87,000.

Nature News, 7<sup>th</sup> October 2010

## UK/USA: ATLA gets ARDF award

FRAME's scientific journal, ATLA (Alternatives to Laboratory Animals), has been presented with a \$ 5,000 award by an American alternatives organisation, in recognition of its influence in promoting the orderly replacement of animal experimentation. The William and Eleanor Cave Award has previously always been given to American individuals, but the awarding body, the Alternatives Research & Development Foundation (ARDF), wanted to stress ATLA's importance in the USA. ARDF President Sue Leary said: "ARDF has decided to do some-

thing a little unusual this year and present the award to a journal. In the past it has been awarded to people, especially scientists and science or medical educators who have made significant contributions to the field of alternatives. The award points to ATLA's 'lifetime achievements' in helping to create, nurture and sustain an international community of people interested in alternatives. Its impact was felt in the USA at a time when we were still finding our way."

Prof. Michael Balls, Chairman of the FRAME Trustees and Editor of ATLA,

received the award at a reception during the 2010 In Vitro Alternatives Forum, organised in Alexandria, Virginia, by the Institute for In Vitro Sciences.

It has long been FRAME policy to subsidise ATLA distribution to interested parties in countries where the concept of replacement of animals in medical and scientific experiments is new or underdeveloped. The \$ 5,000 prize will help FRAME to continue that policy.

Press release FRAME,  
29<sup>th</sup> October 2010

The ALTEX editorial staff congratulates its "sister journal" on this success.

## USA: News from NICEATM and ICCVAM

We are pleased to provide this update on recent and planned activities of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). ICCVAM is an interagency committee composed of representatives from the 15 U.S. Federal regulatory and

research agencies that require, use, or generate toxicological and safety testing information. ICCVAM is charged by law to perform technical evaluations of the usefulness and limitations of new, revised, and alternative test methods with regulatory applicability, and to provide recommendations on their scientific validity to U.S. Federal Agencies. ICCVAM promotes the scientific validation and regulatory ac-

ceptance of toxicological and safety testing methods that more accurately assess the safety and 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 safety testing methods. NICEATM and ICCVAM collaborate to evaluate new and improved test methods applicable to the needs of U.S. Federal agencies, and work to achieve national and international harmonization of safety testing methods.

### **ICCVAM recommends more humane eye safety testing**

ICCVAM recently forwarded final evaluation reports and recommendations to U.S. agencies on alternative safety testing methods and strategies to identify the potential of chemicals and products to cause eye injuries. ICCVAM recommends the routine use of anesthetics, analgesics, and humane endpoints whenever animals must be used for eye safety testing. ICCVAM also provided recommendations for several *in vitro* safety testing methods and a testing strategy proposed for identifying eye safety hazards without using animals. Adoption and implementation of these ICCVAM recommendations will contribute to more humane and reduced animal use for required product safety testing, while continuing to protect public health.

ICCVAM recommends that pain management procedures should always be used whenever it is necessary to use rabbits for eye safety testing required by regulatory agencies. The ICCVAM evaluation report includes a test method protocol that describes how to use topical anesthetics (similar to those used in human eye surgeries) and systemic analgesics prior to and after test article administration in order to avoid or minimize animal pain and distress. The report also identifies specific clinical signs and lesions that, if observed during animal testing, can be used as humane endpoints to allow the investigator to end a study early in order to reduce or avoid potential animal pain and distress.

ICCVAM also recommends that the Cytosensor microphysiometer (CM) test method can be used as a screening test to identify some types of water-soluble substances that may cause permanent or severe eye injuries. Test substances within a defined limited applicability domain (i.e., water soluble substances and mixtures) that are positive in the CM test method

can be classified as having the potential to cause severe or permanent eye injuries without additional testing using animals. The CM test method can also be used, with an even more restricted applicability domain (i.e., water soluble surfactants and surfactant-containing formulations), to determine that chemicals and products do not cause eye injuries that are severe enough to require eye hazard labeling. If accepted by Federal agencies, the CM test method will be the first *in vitro* test method available in the U.S. for this purpose. However, a chemical that produces a response in the CM test method between these two extremes would require additional testing (*in vitro* and/or *in vivo*) to establish a definitive classification. The CM test method is not considered appropriate for the identification of mild or moderate ocular irritants.

ICCVAM evaluated four other *in vitro* test methods (the bovine corneal opacity and permeability, hen's egg test – chorioallantoic membrane, isolated chicken eye, and isolated rabbit eye test methods) for their usefulness and limitations for identifying substances with the potential to cause nonsevere and reversible ocular injuries and substances that do not require ocular hazard labeling. ICCVAM concluded that the predictivity of these methods must be improved before they can be used in regulatory safety testing to classify such substances.

ICCVAM also evaluated and developed recommendations on use of an *in vitro* ocular safety testing strategy proposed for characterizing eye injury hazards for products used as antimicrobials regulated by the U.S. Environmental Protection Agency (EPA). While some of the methods appear promising, ICCVAM concluded that there is currently insufficient data with which to adequately demonstrate that the proposed strategy can classify test substances to the appropriate EPA ocular category, and recommended that further studies are needed.

Finally, ICCVAM recommended that a proposed low volume rabbit eye test (LVET) should not be used for future regulatory testing due to performance issues when compared to the current standard rabbit eye test. However, ICCVAM concluded that data from past studies that

used the LVET can be used in a weight-of-evidence approach to classify ocular hazards.

Four recently published ICCVAM test method evaluation reports include the ICCVAM recommendations, ICCVAM-recommended protocols, final background review documents, independent peer review panel report, and the data used for the ICCVAM evaluations. The reports and recommendations have been transmitted to Federal agencies for their review and response to ICCVAM in accordance with the provisions of the ICCVAM Authorization Act of 2000, which requires agencies to review the recommendations and respond to ICCVAM within 180 days. Links to these and other ICCVAM recommendations on alternative methods to identify potential eye safety hazards can be found on the ICCVAM website at: <http://iccvam.niehs.nih.gov/methods/ocutox/ocutox.htm>

### **NICEATM and ICCVAM organize international workshop on alternatives for vaccine potency and safety testing**

Nearly 200 scientists from 13 countries gathered last month at the “International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions.” Workshop participants reviewed the current state of the science and availability and recommended future research, development and validation needed to advance alternative methods that can reduce, refine (decrease or eliminate pain and distress), and replace the use of animals for human and veterinary vaccine post-licensing potency and safety testing. The workshop, which took place on September 14-16 at the National Institutes of Health in Bethesda, Maryland, was organized by NICEATM and ICCVAM in partnership with the European Centre for the Validation of Alternative Methods, the Japanese Center for the Validation of Alternative Methods, and Health Canada. The workshop was co-sponsored by the Society of Toxicology.

The workshop participants identified knowledge and data gaps that need to be addressed to develop methods that can



further reduce, refine, and replace the use of animals in vaccine testing. Participants also identified and prioritized research, development, and validation activities needed to address these knowledge and data gaps, including the application of new science and technology to develop improved methods. They agreed that vaccines that use the largest number of animals and that are associated with the greatest pain and distress should be given the highest priority for development and validation of alternative test methods. Participants also emphasized the need to find ways to avoid or minimize testing with live viruses and bacteria that are hazardous to workers. Ways to promote the increased use of accepted methods were also discussed. Implementation of the workshop recommendations is expected to advance the availability of alternative methods for vaccine potency and safety testing while ensuring continued protection of human and animal health.

Representatives from the U.S. Food and Drug Administration and U.S. Department of Agriculture joined scientists from Health Canada, the United Kingdom, Japan, and the World Health Organization to discuss their regulatory processes for evaluating human and veterinary vaccines. Although there are differences in these processes, each requires potency testing to ensure that each lot of a vaccine maintains the antigenic characteristics that make it effective, and safety testing to prevent the release of vaccine lots that might cause serious adverse health effects.

The workshop provided a unique opportunity for stakeholders from the human and veterinary vaccine sectors to interact and gain important insights on similarities and differences in how potency and safety testing is currently conducted in each sector. Invited participants included scientists from five U.S. Federal agencies as well as representatives from the governments of Japan, Canada, the United Kingdom, the Netherlands, and the European Union. National and multinational corporations and research institutions were also represented.

Presentations from the workshop are available on the NICEATM-ICCVAM website at: <http://iccvam.niehs.nih.gov/meetings/BiologicsWksp-2010/Biologics->

[Wksp.htm](#). Complete proceedings of the workshop, including manuscripts from speakers and breakout group sessions, will be published next year as a dedicated issue of *Procedia in Vaccinology*. An article summarizing the workshop discussions and conclusions will also be published in the journal *Biologicals*. The conclusions and recommendations resulting from the workshop will be provided to ICCVAM for prioritization of future research, development, and validation activities for alternative test methods that reduce, refine, and replace the use of animals in vaccine potency and safety testing.

### **Two ICCVAM workshops on best practices for regulatory safety testing to be held in January 2011**

NICEATM and ICCVAM announce the first two workshops in a planned series on “Best Practices for Regulatory Safety Testing.” The workshops, “Assessing the Potential for Chemically Induced Eye Injuries” and “Assessing the Potential for Chemically Induced Allergic Contact Dermatitis,” are planned for January 19 and 20, 2011, respectively.

The primary objective of these one-day workshops is to assist participants in gaining a practical understanding of the theory and application of available methods that can be used to evaluate the hazard potential of chemicals and products while minimizing animal use and avoiding pain and distress. Participants will learn the strengths and weaknesses of available alternative test methods, become familiar with the types of data they provide, and learn how to use these data in regulatory safety assessments. Topics discussed during these workshops will be of particular interest to those involved in conducting safety tests for chemically induced eye injuries and/or chemically induced allergic contact dermatitis, those responsible for reviewing study protocols prior to testing, and regulators who will review data generated by the tests.

The workshops are free and open to the public with attendance limited only by the space available. Those interested may register to attend one or both workshops. The workshops will be held at the William H. Natcher Conference Center on the

main campus of the National Institutes of Health in Bethesda, Maryland. More information on the workshop, a draft agenda, and a link to an online registration form are available on the NICEATM-ICCVAM website at: <http://iccvam.niehs.nih.gov/meetings/Implement-2011/ImplementWksp.htm>

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

NICEATM and ICCVAM welcome nominations and submissions of new or modified alternative safety testing methods with the potential to reduce, refine, or replace the use of animals while continuing to protect people, animals, and the environment.

- *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 welcome and can be directed to Dr. William S. Stokes, Director, NICEATM, at [niceatm@niehs.nih.gov](mailto:niceatm@niehs.nih.gov)



gov; phone 919-541-2384; fax 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](http://iccvam.niehs.nih.gov/contact/ni_list.htm)

### References for reports mentioned in this update

ICCVAM (2010). ICCVAM test method evaluation report: Recommendations for routine use of topical anesthetics, systemic analgesics, and humane endpoints to avoid or minimize pain and distress in ocular safety testing. *NIH Publication No. 10-7514*. Research Triangle Park, NC: NIEHS. Available: <http://iccvam.niehs.nih.gov/methods/ocutox/OcuAnest-TMER.htm>

ICCVAM (2010). ICCVAM test method evaluation report: Current validation status of in vitro test methods proposed for identifying eye injury hazard potential of chemicals and products. *NIH Publication No. 10-7553*. Research Triangle Park, NC: NIEHS. Available:

<http://iccvam.niehs.nih.gov/methods/ocutox/MildMod-TMER.htm>

ICCVAM (2010). ICCVAM test method evaluation report: current validation status of a proposed in vitro testing strategy for U.S. environmental protection agency ocular hazard classification and labeling of antimicrobial cleaning products. *NIH Publication No. 10-7513*. Research Triangle Park, NC: NIEHS. Available: <http://iccvam.niehs.nih.gov/methods/ocutox/AMCP-TMER.htm>

ICCVAM (2010). ICCVAM test method evaluation report: recommendation to discontinue use of the low volume eye test for ocular safety testing. *NIH Publication No. 10-7515*. Research Triangle Park, NC: NIEHS. Available: <http://iccvam.niehs.nih.gov/methods/ocutox/LVET.htm>

Press release

ICCVAM, September 9, 2010

## USA: NIH statement regarding stay of stem cell injunction

We are pleased with the Court's interim ruling, which will allow promising stem cell research to continue while we present further arguments to the Court in the weeks to come. With the temporary stay in place, NIH has resumed intramural research and will continue its

consideration of grants that were frozen by the preliminary injunction on August 23. The suspension of all grants, contracts, and applications that involve the use of human embryonic stem cells has been temporarily lifted. Human embryonic stem cell research holds the

potential for generating profound new insights into disease, cell-based therapeutics, and novel methods of screening for new drugs.

NIH press release  
10<sup>th</sup> September 2010



# CAATfeed

## **Complete video of CAAT workshop "21<sup>st</sup> Century Validation Strategies for 21<sup>st</sup> Century Tools" available online**

The CAAT workshop, 21<sup>st</sup> Century Validation Strategies for 21<sup>st</sup> Century Tools, was held July 13 and 14, 2010, in Baltimore, Maryland. The full listing of speakers and topics, along with Quicktime video of the event is available on the CAAT website at <http://caat.jhsph.edu/programs/workshops/july13validation.htm>.

## **Nanotechnology and nanomaterials: Addressing challenges to safety assessment and regulation**

On October 11-13, CAAT held a workshop on nanotechnology to discuss the development of a science-based strategy for testing nanomaterials that can provide the information needed for informed decision making and for the selective development of new products with optimal risk-benefit considerations. A report will be forthcoming.

## **Critical evaluation of the use of dogs in biomedical research & testing: A CAAT workshop**

On January 12 and 13, 2011, CAAT will hold a workshop bringing together investigators who use dogs as disease models to present their research while fostering dialogue on the implementation of alternative models. Representatives from the US Food and Drug Administration (FDA) will be invited to review data obtained from dogs submitted in support of drug submissions. Veterinarians and experts in dog behavior will be invited to discuss the welfare issues associated with research and testing on dogs.

The workshop will take place at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. Further details will be posted on the CAAT website: <http://caat.jhsph.edu>

For more information contact Joanne Zurlo, CAAT Director of Science Strategy ([jjzurlo@jhsph.edu](mailto:jjzurlo@jhsph.edu)).

## **Joint CAAT-Europe / ecopa – Workshop: Implementation of the new EU Directive 2010/63/EU on the protection of animals used for scientific purposes: Opportunities for the 3Rs**

To be held January 31 - February 2, 2011 in Berlin, Germany.

*Aim:* To bring together key stakeholders from various EU Member States to reach common ground for steps to be taken with regard to the implementation of individual articles of the new Directive with an impact on 3Rs research, validation, funding and dissemination.

Now, after years of negotiation, the new EU Directive on the protection of animals used for scientific purposes 2010/63/EU will come into force 20 days after publication in the Official Journal of the European Union. Member States have to implement this piece of legislation within two years time.

### *Structure:*

- 1<sup>st</sup> day: half day open to public and media; key presentations about 3Rs aspects of the Directive (EU-Commission, stakeholders)
  - 2<sup>nd</sup> day: full day for discussions and drawing up of the major issues and possible future actions
  - 3<sup>rd</sup> day: production of a consensus paper with conclusions and recommendations
- Participants (workshop part by invitation only):*
- Representatives of the national consensus platforms (members of ecopa) from academia, animal welfare, government, and industry.
  - EU officials
  - Scientists/representatives of science organizations dealing with 3Rs issues

### *Additional information:*

- Venue (hotel in the centre of Berlin) sponsored by CAAT-Europe, including travel reimbursement of invited participants.
- Invitations will be processed (also) through the ecopa network for outreach into various Members States and stakeholder forums.

See also Food for Thought article, *Comparative analysis of the revised Directive 2010/63/EU for the protection of laboratory animals with its predecessor 86/609/EEC – a t<sup>4</sup> report*, by CAAT Director Thomas Hartung: [http://www.altex.ch/resources/altex\\_2010\\_4\\_285\\_303\\_Hartung5.pdf](http://www.altex.ch/resources/altex_2010_4_285_303_Hartung5.pdf)

Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (Text with EEA relevance) <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:EN:PDF>

## **t<sup>4</sup> workshops planned**

Within the Center for Alternatives to Animal Testing – Europe (CAAT-Europe) and the framework of the transatlantic think tank for toxicology (t<sup>4</sup>)

## **Biomarkers in *in vitro* systems: Selection of the most appropriate *in vitro* assays and their use in hazard and risk assessment: January 2011**

*Goal of the workshop:* This workshop aims at an in-depth exploration of the possibilities of using *in vitro* biomarkers for toxicity in the risk assessment process.

## **Recent Publications**

Hogberg, H. T., Sobanski, T., Novellino, A. et al. Application of micro electrode arrays (MEAs) as an emerging technology for developmental neurotoxicity: evaluation of domoic acid-induced effects in primary cultures of rat cortical neurons. *NeuroToxicology*, in Press, doi:10.1016/j.neuro.2010.10.007.