CH: *In vitro veritas* in Geneva, Switzerland

Pierre Cosson, the new Doerenkamp-Naef-Zbinden Professor at the University of Geneva held his inauguration lecture entitled "*In vitro veritas: Un système immunitaire dans un tube à essai*" on his test tube research, on March 5, 2009.

The talk, given at the University of Geneva Medical Centre, auditorium C150, started at 12.30 pm. But the first official sentence the dean of the faculty medicine, Prof. Jean-Louis Carpentier, said was: "We must move!" The auditorium was too small relative to the great interest in the inauguration of Pierre Cosson. After moving to a bigger auditorium about 250 guests listened to the introductory speeches of the dean and Egon Naef, president of the Egon-Naef Foundation, who described the inception of the chair and introduced all the sponsors (and also those who gave nothing).

In his lecture, Pierre Cosson gave insight into his research on a soil amoeba. In the study of bacterial infectious diseases, it is essential to test a bacterium's capability to cause a disease. Usually, a host is infected, typically a mouse, and one allows the disease to progress. Cosson is working on a new system in which mice are replaced by a non-mammalian host, *Dictyostelium discoideum*, a soil amoeba. Very similar results to those in mammalian hosts are obtained in this system. Cosson now aims to extend these results to validate this system as an alternative to mammalian models.

His laboratory also studies ways to produce disease-fighting antibodies in a test tube instead of by using animals. These are essential research tools in many research laboratories, but the techniques are more complex. Developing these techniques in Geneva would greatly benefit researchers at the university and at institutions outside Geneva and Switzerland. The Doerenkamp-Zbinden chairs in Baltimore, Konstanz and Utrecht want to take over this technique as soon as possible. Before coming to the University of Geneva, Cosson worked at the Roche Institute of Immunology in Basel. So, his extensive expertise in immunology will serve him well in this quest for a novel system to produce antibodies *in vitro* instead of in rabbits. On the date of the inauguration ceremony, the president of the Doerenkamp-Zbinden foundation, Franz P. Gruber, was pleased to inform Pierre Cosson that the foundation board had decided to sponsor this antibody project with additional funding. See also news about this project.

fpg

CH: *In vitro* selection of antibodies: a new gold standard

Antibodies are the most commonly used reagent to detect a given protein in a complex mixture. They are used in almost every biology laboratories around the world to detect the presence of a protein, to localize it in a cell or in a tissue, or to purify it. Specific antibodies are obtained by immunizing rabbits or mice, and this leads to the use of thousands of animals every year.

A promising alternative has been developed over the last decades often referred to as recombinant antibodies or phage display technology. Using advanced molecular biology techniques, specific antibodies can be selected *in vitro*, then produced in unlimited amounts in bacteria. No animal is required at any step of the procedure. This technique has many practical advantages compared to the use of animals: the antibodies are produced faster (a few weeks), in better-controlled conditions, at a low cost, and these reagents are much easier to handle than classical antibodies. This is a clear case where ethical considerations (sparing the live of animals) can be reconciled with the need to advance biomedical knowledge.

Why then hasn't this technology completely replaced the use of animal immunization? Probably the main reason is that this technique requires a real know-how, as well as a few specific procedures. Individual laboratories, requesting a few new antibodies every year, cannot spend a significant part of their resources to learn this new approach. The consequence is that only a few laboratories in the world actually make use of this technique, while most still make use of animals.

In Geneva, the Doerenkamp-Naef-Zbinden Chair is trying to change this. The DNZ Chair is starting a new project to develop this technology at the Faculty of Medicine, and make it accessible to all interested researchers in our University. Our hope is that within a few years, this technique will become the new gold standard for the production of antibodies, and will largely replace the use of animals, especially rabbits. If this program is a success, it may then be duplicated in other countries. This project is developed with the support of the Doerenkamp-Zbinden Foundation.

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EU: Acceptance of a new *in vitro* skin irritation method

At its 30th meeting, held on 9 and 10 March 2009, the non-Commission members of the ECVAM Scientific Advisory Committee (ESAC) unanimously endorsed the following statement:

1. Performance of the ECVAM-validated skin irritation *in vitro* tests under UN GHS

Up to date, three reconstructed human epidermis models (the EpiSkin, the modified EpiDerm and the SkinEthic test methods) have been validated by ECVAM primarily according to the EU classification system. Importantly, the study was designed in view of the upcoming UN GHS system, e.g. with respect to the selection of test substances. Upon completion of the ECVAM Skin Irritation Validation Study (SIVS, Ref. 1) the EpiSkin test method was found to be a reliable and relevant stand-alone method (ESAC statement from April 2007, Ref. 2) and, hence, its performance as reference method was used for specifying the ECVAM skin irritation Performance Standards in May 2007. The modified EpiDerm and the SkinEthic test methods were subsequently validated on the basis of these Performance Standards using the 20 defined Reference Chemicals (ESAC statement from November 2008, Ref. 3).

In December 2008, the EU adopted the UN Globally Harmonised System for Classification and Labelling and will implement this by means of the so-called CLP regulation (Regulation EC 1272/2008, Ref. 4). The new EU classification system based on UN GHS (abbreviated here as "GHS-EU") continues to use two categories to distinguish non-irritant (no-category) from irritant (category 2) substances. However, according to the new rules for skin irritation classification and labelling, the cut-off score to distinguish between no-category and category 2 substances was shifted to 2.3 from a value of 2.0 (EU classification system). Consequently substances with an *in vivo* score between 2.0 and 2.3 that are considered irritant under the existing EU classification system will be considered non-irritants under the future GHS-EU classification system, which does not use the optional UN GHS category 3.

The performance of all three tests under GHS-EU has now been calculated taking this shift of the cut-off value into consideration. The performance of all three methods also under GHS-EU has been found satisfactory (Tab. 1). While the specificity of the EpiSkin method is decreased from 81.8%* (EU system) to 71.1%* (GHS-EU system), the test sensitivity has increased from 72%* (EU system) to 84.6%* (GHS-EU system). The two other methods show similar values for the specificity (both tests 69.2%*) and higher sensitivity values than the reference method under GHS-EU.

The original ESAC statements relating to these test methods therefore continue to be accurate with respect to the scientific validity of the methods also under the GHS-EU classification system. Updated accuracy values under GHS-EU are provided in this statement

Moreover, on the basis of the documentation available and due to the overall satisfactory performance of the three methods, the ESAC is of the opinion that no further work is required at this stage and that the existing information on the validation studies and additionally available background information is sufficient to explain the changes in performance of the tests and key aspects of the performance standards (i.e. reference chemicals and defined accuracy values) necessitated by the threshold shift upon adaptation of the GHS system in the EU. As is common practice, adaptations to technical progress

Tab. 1: Accuracy values for the three ECVAM-validated skin irritation *in vitro* test methods under GHS-EU

	EpiSkin test method (58 chemicals[1])	EpiSkin test method (20 reference chemicals)	Modified EpiDerm test method (20 reference chemicals)	SkinEthic test method (20 reference chemicals)
Specificity (%)[2]	71.1	76.9	69.2	69.2
Sensitivity (%)[2]	84.6	85.7	85.7	100
Overall Accuracy (%)[2]	74.1	80	75	80

[1] The test substances from the ECVAM Skin Irritation Validation Study (SIVS) conducted from 2003 to 2007.
[2] Based on the median (or mode) of the individual laboratory predictions.

*) all values are based on the median ("final call") on the median of the individual laboratory predictions. Since these are categorical values (either 1 or 0 = positive or negative) both, mode and median can be used for the derivation of the final call

should be performed as appropriate and necessary. It should be noted, that any conclusions on the applicability domain are based, at this stage, mainly on the testing set used during the ECVAM SIVS.

2. Adaptation of the reference chemicals and defined accuracy values of the ECVAM Performance Standards

2.1 Updated list of reference chemicals

Due to the threshold shift according to the adoption of the UN GHS system in the EU, the reference chemicals of the ECVAM Performance Standards were not any longer balanced with regard to an equal representation of Irritant *versus* non-irritant substances.

To address this and other issues (i.e. global commercial availability, evidence that some substances are non-irritant in human, handling qualities) the reference chemical set was updated. The updated reference chemical list reflects the false negative and false positive rates obtained with the EpiSkin method under GHS on the basis of the full set of 58 test substances from the ECVAM skin irritation validation study allowing for the appropriate future validation of modified or similar ("me-too") test methods.

Deletions

The following six substances were deleted (*in vivo* scores in paratheses):

1) d-propylene glycol (0)
2) allyl heptanoate (1.7)
3) terpinyl acetate (2.0)
4) tri-isobutyl phosphate (2.0)
5) alpha-terpineol (2.7)
6) butyl methacrylate (3.0)

Additions

The following six substances were added (*in vivo* scores in paratheses):

1) cinnamaldehyde (2.0)
2) 2-chloromethyl-3,5-dimethyl-4-methoxypyridine HCl (2.7)
3) 5% potassium hydroxide (3.0)
4) benzenethiol, 5-(1,1-dimethyl)-2 methyl (3.3)
5) 1-methyl-3-phenyl-1-piperazine (3.3)
6) 1,1,1-trichloroethane (4.0)

Moreover, the updated reference chemicals (Tab. 2) meet the following criteria:

1) the chemicals are commercially available
2) they are representative of the full range of Draize irritancy scores (from non-irritant to strong irritant)
3) they have a well-defined chemical structure
4) they are representative of the chemical functionalities used in the validation process
5) they are not associated with an extremely toxic profile (e.g. carcinogenic or toxic to the reproductive system) and they are not associated with prohibitive disposal costs.

2.2 Updated defined accuracy values as specified in the ECVAM skin irritation Performance Standards

Based on the performance of the validated reference method EpiSkin with the up-

Tab. 2: Updated reference chemicals

Nr.	Chemical	*In vivo* Score	EU *in vivo* category	GHS-EU *in vivo* category	EPISKIN classification
1	1-bromo-4-chlorobutane	0	no	no category	**I**
2	diethyl phthalate	0	no	no category	NI
3	naphthalene acetic acid	0	no	no category	NI
4	allyl phenoxy-acetate	0.3	no	no category	NI
5	isopropanol	0.3	no	no category	NI
6	4-methyl-thio-benzaldehyde	1	no	no category	**I**
7	methyl stearate	1	no	no category	NI
8	heptyl butyrate	1.7	no	optional cat. 3	NI
9	hexyl salicylate	2	R38	optional cat. 3	NI
10	cinnamaldehyde	2	R38	optional cat. 3	I
11	1-decanol *	2.3	R38	category 2	I
12	cyclamen aldehyde	2.3	R38	category 2	I
13	1-bromohexane	2.7	R38	category 2	I
14	2-chloromethyl-3,5-dimethyl-4-methoxypyridine HCl	2.7	R38	category 2	I
15	5% potassium hydroxide	3	R38	category 2	I
16	di-n-propyl disulphide *	3	R38	category 2	**NI**
17	benzenethiol, 5-(1,1-dimethylethyl)-2-methyl	3.3	R38	category 2	I
18	1-methyl-3-phenyl-1-piperazine	3.3	R38	category 2	I
19	heptanal	4	R38	category 2	I
20	1,1,1- trichloroethane	4	R38	category 2	I

*) Substances which are irritant in the rabbit but for which there is reliable evidence that they are non-irritant in humans.

Tab. 3: Defined Accuracy Values

	Defined Accuracy Values
Specificity (%)	**70**
Sensitivity (%)	**80**
Overall Accuracy (%)	**75**

dated reference chemicals and additional considerations relating to the relevance in the species of interest, the defined accuracy values are given in Table 3.

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REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006)

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10th March 2009

EU: Ban on acute toxicity tests on animals for cosmetics ingredients

The ban on seven toxicity tests for cosmetics ingredients came into force on the 11th of March 2009. This second deadline of the 7th amendment to the European Union's Cosmetics Directive outlaws the use of any ingredients that have been tested for acute toxicity in animals after this cut-off date in any beauty products or toiletries as well as the import of cosmetics containing ingredients that were tested for acute toxicity in animals anywhere in the world into the EU.

Two thousand cosmetics manufacturers in the European Union sell about 5 billion items per year with a total value around € 80 billion. Although this sector has only reported using relatively few animals in recent years, about 0.05% of the total number used in regulatory testing in 2005, it has been able to buy in new ingredients previously tested in animals by chemicals manufacturers until the ban came into force.

The tests falling under the ban are for skin irritancy, sensitivity to light, corrosivity, absorption through the skin, genetic toxicity, eye irritancy and acute toxicity. Although alternative assays have only been fully validated by the European Center for Validation of Alternative Methods and the Organization for Economic Co-operation and Development for four of these seven tests to date, the validation of alternatives for the three remaining assays is foreseen in the next couple of years.

A further deadline is currently set for the 11th of March 2013, when all long-term toxicity tests on animals for cosmetics ingredients will also be banned, making the development of new cosmetics in Europe animal-free. However, as progress in replacing these tests is much slower, owing to the difficulties of simulating these long-term processes *in vitro*, this deadline may still be renegotiated. For an in depth discussion, see "Food for thought...on alternative methods for cosmetics safety testing", *ALTEX 25, 3/08*, 147-162.

sva

EU: EDQM accepts alternative to rabbit pyrogen test

The European Directorate for the Quality of Medicines and Health Care (EDQM, Council of Europe) is a European organisation involved in the harmonisation and co-ordination of standardisation, regulation and quality control of medicines, blood transfusion, organ transplantation, pharmaceuticals and pharmaceutical care. The EDQM reports that the European Pharmacopoeia Commission has adopted a new general chapter on monocyte activation tests: the chapter provides *in vitro* alternatives to the rabbit pyrogen test and will hopefully contribute to the reduction of use of laboratory animals, see press release at: www.edqm.eu/medias/fichiers/133rd_Session_of_the_Eu.pdf

A comment by the Paul-Ehrlich Institute in Langen, Germany, reads, "Finally, after more than 10 years of development, validation, optimisation, consultation, persuasion (and some frustration in between) the Monograph 2.6.30. "Monocyte-Activation test" (formerly known as "alternative pyrogen test") was adopted by the European Pharmacopeia Commission during the 133rd session in March 2009. The Monograph will be implemented into the European Pharmacopeia in 2010. The Monograph describes three different general approaches (quantitative test, limit test, batch-to batch comparison) for Monocyte Activation tests. The unresting efforts of many people were crowned with success. Besides the enormous input of scientific colleagues and their staff (including our own group) the PEI has to highlight the extraordinary support by the German Pharmacopoeia Commission."

ALTEX is proud that it was the first journal to publish an article on one of these new tests in the issue 2/1995: Thomas Hartung and Albrecht Wendel: Detection of pyrogens using human whole blood, *ALTEX 12*, 70-75. But, in the opinion of ALTEX, 14 years between publishing a new test principle and implementing it in the European Pharmacopoeia is far too long and has resulted in thousands of rabbits being used unnecessarily.

fpg

GER: Doctors against animal experimentation see opportunities in the revision of 86/609

The association Doctors Against Animal Experiments Germany demands a clear commitment to animal-free research and a renunciation of animal experiments on occasion of the current polls on the EU and state level on the content of the EU directive on animal experiments*. "Politics now has its opportunity to do its duty and embark on consequently ethical and scientifically sound pathways that do not cause suffering to animals" explains biologist Silke Bitz, scientific officer of the association.

In their statement, the Doctors Against Animal Experiments Germany ask of politics that the content of proposals for animal experiments is made available to the public and that quality control measures are introduced, which evaluate all projects involving animal experiments retrospectively. Further, the association demands that animal-free research be given the highest priority. Experiments on primates should be banned without exception. "The revision of the directive should be viewed as a chance to set a clear course towards abandoning the socio-politically unacceptable animal experiment in a timely manner," continues Bitz.

Only a few days ago, the upper house of German parliament (Bundesrat) made a recommendation to the German federal government to considerably weaken the Commission's draft to the detriment of animal protection. The Doctors' association calls upon the German Minister for Agriculture Ilse Aigner not to bow to the lobby that benefit from animal experiments and to stand against any relaxation of the draft that would cement unethical and unscientific methods.

Currently, the European Parliament and the European Council of Ministers, in which Minister Aigner represents the German government, are voting on the Commission's draft for the revision of the directive. In the next days, the Committees on Environment and on Industry of the European Parliament will convey their positions to the Committee on Agriculture, which is responsible for drafting the European Parliament's statement on the Commission's draft. The vote of the Committee on Environment on 18.02.09 was sobering according to the Doctors Against Animal Experiments, as numerous suggestions for improvements for the animals did not find a majority. On 31.03.09 the Committee on Agriculture will vote on the positions of both committees, and the vote in the plenum will take place on 04.05.09.

In 2005 more than 12 million animals were used in experiments in the EU; at the last count in 2007, more than 2.6 million animals were used in Germany alone.

Historische Chance für eine Weichenstellung
www.aerzte-gegen-tierversuche.de,
translated by SvA

* Directive 86/609/EWG of the 24th of November 1986 on the protection of animals used for experimental and other scientific purposes

GER: Ursula M. Haendel Prize 2009 goes to Hannover

The haematologist, Professor Christopher Baum, and his coworkers, Dr. Ute Modlich and Sabine Knöß, received the Ursula M. Haendel Animal Protection Prize 2009. The prize was awarded to the research team from the Hannover Medical School (MHH) for a novel test system for the development of gene therapies, which can reduce the number of necessary animal experiments considerably. The Ursula M. Haendel Animal Protection Prize is awarded by the German Research Council (DFG) to scientists who strive for the improvement of animal protection in science in an exemplary and enduring manner. The prize was awarded for the third time since its inception in 2004 and is endowed with 50,000 Euro.

SvA

GER/USA: Standardisation adulterates animal experiments

Under the title "Environmental standardization: cure or cause of poor reproducibility in animal experiments?" S. Helene Richter, Joseph P. Garner and Hanno Würbel published in Naturemethods a very intersting paper in which they come to the finding that environmental standardisation is a cause of, rather than a cure for, poor reproducibility of experimental outcomes. Environmental standardisation can contribute to spurious and conflicting findings in the literature and unnecessary animal use. They demand that more research should be invested into practicable and effective ways of systematic environmental heterogenisation to attenuate these scientific, economic and ethical costs.

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NATURE METHODS 6/4, April 2009, p257ff

NI: Scientists confirm crab's memory of pain

New research published by a Queen's University Belfast academic shows that crabs not only suffer pain, but that they also retain a memory of it. The study, which looked at the reactions of hermit crabs to small electric shocks, was carried out by Professor Bob Elwood and Mirjam Appel from the School of Biological Sciences at Queen's and was published in the journal Animal Behaviour. Professor Elwood, who previously carried out a study showing that prawns feel pain, said his research highlighted the need to investigate how crustaceans are treated in the food industry.

Hermit crabs have no shell of their own, so they inhabit other structures, usually empty mollusc shells. Wires were attached to shells to deliver small shocks to the abdomen of some of the crabs within the shells. The only crabs that left their shells were those that had received shocks, indicating that the experience was unpleasant for them. This shows that central neuronal processing occurs rather than the response merely being a reflex.

The main aim of the experiment, however, was to deliver a shock just under the threshold that causes crabs to leave their shells to see what happened when a new shell was then offered. Crabs that had been shocked but had remained in their shell appeared to remember the experience of the shock, because they quickly moved towards the new shell, investigated it briefly, and were more likely to change to the new shell compared to those that had not been shocked.

Professor Elwood said that there has been a long debate about whether crustaceans, including crabs, prawns and lobsters, feel pain. This research demonstrates that it is not a simple reflex, but that crabs trade off their need for a quality shell with the need to avoid the harmful stimulus. Such trade-offs are seen in vertebrates, in which the response to pain is controlled with respect to other requirements. Humans, for example, may hold on to a hot plate that contains food, whereas they may drop an empty plate, showing that humans take differing motivational requirements into account when responding to pain. Trade-offs of this type have not been previously demonstrated in crustaceans.

The results are consistent with the idea of pain being experienced and remembered by these animals. According to Professor Elwood, in contrast to mammals, little protection is given to the millions of crustaceans that are processed in the fishing and food industries each day. It was added that more research is needed in this area, where a potentially very large problem is being ignored. With vertebrates one is asked to err on the side of caution, and this is certainly the approach that should also be taken with these crustaceans.

Queen's University Belfast press release from 27th March 2009

OECD: Experts approve new test guidelines for acute inhalation toxicity

On April 9, 2009, the OECD Environment, Health and Safety Directorate approved several important documents on acute inhalation toxicity testing, which will considerably reduce both experimental animal numbers and their suffering. The new tests follow the approach that was successfully established for acute oral toxicity testing and consist of the following documents:

1. OECD Guidance Document (GD) 39 on "acute inhalation toxicity testing"
2. a revised Test Guideline (TG) 403 Acute Inhalation Toxicity
3. a new TG 436 Acute Inhalation Toxicity - Acute Toxic Class (ATC) Method

The three documents were approved by the national coordinators of the OECD Environment, Health and Safety programme at their last meeting in March and will be available on the OECD website shortly (www.oecd.org/ehs/).

The USA, represented by the EPA, and Germany, represented by the BfR (Federal Institute for Risk Assessment), were the lead countries driving this important initiative, which was brought to a successful conclusion after several years of very intense discussions among international experts. John Whalan (US EPA) and Juergen Pauluhn (BayerSchering AG, Germany) were the main contributors, who helped to get the new testing strategy, which is outlined in the new OECD Guidance Document 39 on "acute inhalation toxicity testing" (see website), accepted.

Most importantly, no experimental validation studies had to be performed since a biostatistical performance assessment funded by the BfR under the chairmanship of Matthias Greiner (BfR) proved that the Acute Toxic Class (ATC) method, which uses a significantly lower number of animals, allows the correct classification of the acute inhalation toxicity of chemicals.

In contrast to the case of acute oral toxicity testing, the classical OECD TG 403 "Acute Inhalation Toxicity" was not abandoned, since it still has to be performed for hazard assessment under a few well-defined circumstances, e.g. when a population is accidentally exposed to an unknown poisonous gas. However, TG 403 has been updated in many aspects.

The final approval of the new DG 39 and the 2 TGS will still have to undergo several formal procedures within the OECD approval process, which may be achieved by the fall of 2009.

hsp

UK: NC3Rs event marks 50th anniversary of the 3Rs

The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) held an event sponsored by Lord Sainsbury, former Minister of State for Science and Innovation, at the House of Lords in Westminster, London, on the 25th of March 2009 as one of its activities to mark the 50th anniversary of the 3R's. The latest 3Rs research was presented in the form of poster presentations by scientists from academia and industry to an invited audience of members of parliament, peers and other key stakeholders. Three prizes of £ 3,000 each were awarded for the best posters in the categories Replacement, Refinement and Reduction. These described the development of a 3D model of breast cancer, the use of dried blood spots for the generation of toxicokinetic data, and an approach to use fewer animals in an obesity research model, respectively. The event was publicised by a press release and an abstract booklet describing the presented work.

sva

UK: Becoming conscious about fish conscience

In this age of aquaculture the question of fish welfare finds increasing limelight in both the public and political domains. During the race of global aquaculture industries, fish welfare needs have been left behind. However, in the last decade the welfare of fish has become a high-priority issue on political grounds. In 1997, the Treaty of Amsterdam agreed that throughout the EU the concept of welfare is the same in fish as it is in mammals and birds and necessary protection should be applied. More recently, the OIE (World Organisation for Animal Health) announced its plan to harmonise standards throughout its 172 member countries.

Following a request from the European Commission the Animal Health and Welfare (AHAW) panel was asked to deliver a Scientific Opinion on welfare aspects of husbandry systems for farmed fish. The opinion tried to identify their capacity to experience pain, fear and distress, whilst taking into account expressions of sentience.

While for a long time it was believed that fish did not possess complex emotions, new research has highlighted dynamic social functions and environmental responses, whilst issues of fish stress and disease has been forced into the limelight due to the damaging repercussions they can have on the industry.

"As for all animals it is impossible to find one single measurement or welfare indicator that will cover all possible husbandry systems, farmed species and situations," says the AHAW Scientific Opinion. "A range of welfare indicators should be considered when welfare is being evaluated."

Fish in a natural habitat display complex swimming, feeding, anti-predator and reproductive behaviours that are often lacking in fish farms. Fish farmers themselves have witnessed how prolonged exposure to stressors can lead to maladaptive effects or chronic stress. Chronic stress responses that can indicate poor welfare conditions include reduction in immune function, disease resistance, growth and reproduction and even result in death. Fin condition and parasite load are clear and comparable indications that are often associated with poor welfare.

However, indicators of condition do not necessarily show whether a fish is undergoing real feelings of pain, but while some scientists say that fish lack a biological capacity to experience the world in the same way that we do, there is a growing body of evidence to suggest that biological responses are much more similar than previously believed. According to the AHAW Scientific Opinion, there is scientific evidence to support the assumption that some fish species have brain structures potentially capable of experiencing pain and fear.

In the context of welfare of farmed fish the physiological, biochemical and behavioural reactions of fish are considered to be part of the experience of pain, fear and distress – and whilst the extent to which feelings of pleasure exist in fish is unknown – the hormone oxytocin, associated with pleasure in humans and other mammals – occurs in fish.

It seems that we may never truly know how complex the emotional life of a fish may be – but the same may be said of terrestrial animals and even the people whom we feel the closest to.

Adopted and shortened by gk,
full article at
The Fish Site, Adam Anson,
March 2009
http://tinyurl.com/dgw44h

USA: New EPA strategic plan for evaluating the toxicity of chemicals

The US Environmental Protection Agency posted the final version of its new "Strategic Plan for Evaluating the Toxicity of Chemicals" on March 25 at http://www.epa.gov/osa/spc/toxicitytesting/docs/toxtest_strategy_032309.pdf.

The EPA's overview of this document (http://www.epa.gov/osa/spc/toxicitytesting/index.htm) notes that "the traditional risk assessment approach relies heavily on data generated through the intentional dosing of experimental animals." The EPA strategic plan describes a new approach which is based on "advances in molecular biology and computational sciences to transform toxicity testing and risk assessment practices."

The first of three interrelated components in the strategic plan deals with "toxicity pathways identification and use of this information in screening and prioritization of chemicals for further testing." The approach proposed is based on the EPA-commissioned NRC report "Toxicity Testing in the 21st Century: a Vision and a Strategy" (2007) (http://books.nap.edu/catalog.php?record_id=11970). The other components in the EPA plan involve "the use of toxicity pathways information in risk assessment," and "the institutional transition necessary to implement such practices across EPA."

The EPA claims the new approach to toxicity testing and risk assessment should significantly reduce animal testing.

hsp

GER: Gotthard M. Teutsch deceased

Prof. Dr. Gotthard Teutsch passed away on Sunday, 20th of April 2009, aged 90 years after a short, severe illness. For many years Teutsch wrote the Literature Report for ALTEX; he published important assays aiming to improve or sometimes simply soberly contemplating human-animal relationships. Teutsch also established the Archive for Ethics in Animal, Nature and Environmental Protection, which was originally housed in the state library of Baden in Karlsruhe and is now to be found at the Stiftung für das Tier im Recht in Zurich.

A detailed obituary will be included in the first issue of ALTEXethik to be published in autumn 2009. Sadly, Dr. Teutsch will not be able to read this issue himself - he had so looked forward to it.

We extend our heartfelt condolences to his widow.

Franz P. Gruber
for the ALTEX Team

CAATfeed

The Johns Hopkins Center for Alternatives to Animal Testing (CAAT, http://caat.jhsph.edu/) has worked with scientists since 1981 to find new methods to replace the use of laboratory animals in experiments, reduce the number of animals tested, and refine necessary tests to eliminate pain and distress. We are an academic, science-based center affiliated with the Johns Hopkins University Bloomberg School of Public Health. We believe the best science is humane science. Our programs seek to provide a better, safer, more humane future for people and animals.

We provide a variety of resources, including grants for scientists developing non-animal methods, workshops on alternative methods, books, newsletters, and other publications. We also manage **Altweb** (http://altweb.jhsph.edu/), an international online clearinghouse of alternatives news and resources. Altweb has widespread, broad-based international support, working with a Project Team that currently consists of 26-member organizations representing industry, academia, government agencies, animal welfare organizations, and advocacy groups in North America, the European Union, and Asia. Altweb remains the most comprehensive guide to alternatives on the Web, drawing an average of 16,000 unique visitors every month from more than 130 countries. Many additional visitors access the Altweb RSS news feed. New visitors make up 82% of the traffic, indicating a growing interest in alternatives, while researchers and scientists who use the site on a regular basis form a core 12% of visits.

In 2009, Prof. Thomas Hartung became CAAT's new Director, and the inaugural Doerenkamp-Zbinden chair for Evidence-based Toxicology (see also his Food for thought article in this issue of ALTEX). Thomas Hartung was head of ECVAM from 2002 to 2008. Founding Director emeritus, Prof. Alan Goldberg, has transitioned to a new role as Chairman of CAAT's Advisory Board.

ALTEX is now the official journal of CAAT and the **Transatlantic Think Tank of Toxicology (t⁴)** organized by CAAT. With Thomas Hartung as the new North American editor, ALTEX has now expanded to the US and become an international journal for alternative methods. The news corner CAATfeed will keep ALTEX readers informed on CAAT's activities on a regular basis.

CAAT has a new address!
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CAAT's move onto the Johns Hopkins Medical Campus enables us to establish scientific laboratories. Our first focus will be on Developmental Neurotoxicity (DNT). Notably, CAAT organized its second **International Conference on DNT** within CAAT's TestSmart series of workshops in November 2008 in Reston, Virginia. Speaker presentations and meeting abstracts are now posted on the DNT2 page of the CAAT website (http://caat.jhsph.edu/dnt2/program.htm). In addition, for the benefit of stakeholders interested in alternative tests for developmental neurotoxicity (DNT), and in response to the clear desire to continue the dialogue on methods development and use that began at the TestSmart DNT2 meeting, the Steering Committee members have created a DNT Community of Practice Forum, which can be found on the AltTox website at www.alttox.org.

In June 2007, the National Academy of Science (NAS) released its report, **Toxicity Testing and Assessment in the Twenty-first Century**: A Vision and a Strategy (**Tox-21c**). Tox-21c is essentially a roadmap for the future, representing a shift in the current testing paradigm by advocating the utilization of high-throughput, *in vitro* test methods that focus on human rather than animal biology. Current and past members of the CAAT faculty and Advisory Board served on the committee, and CAAT will continue its work as a "champion" of this vision. In March 2009, CAAT hosted a first Tox-21c implementation meeting with representatives from the US and Europe. CAAT is focusing on the implementation of the NAS report in the US and is in the process of setting up a lab, with doctoral students, and post-doctoral fellows at the Johns Hopkins Bloomberg School of Public Health to advance the science necessary to develop evidence-based toxicology and new alternative methodologies.

Concurrently, CAAT Professor Paul Locke, through the **Policy and Outreach Program**, is working to educate legislators about the need for regulatory change and the acceptance of these new methods. The program is organizing a series of five symposia to explore the legal, policy and scientific steps necessary to implement Tox-21c. These symposia, scheduled to begin in summer 2009 and run through fall 2010, will take place in multiple US locations, and Canada, and will target scientists, policy makers, risk assessors, and environmental and animal lawyers and advocates. Each symposium will result in a series of articles for publication in legal, scientific and policy journals. The Outreach Program also includes educational initiatives on Capitol Hill, including a Congressional staff briefing on humane science and the need for global regulatory harmonization scheduled for June, 2009.

CAAT's **research grants program** is the centerpiece of our work, providing critical seed money for scientists to develop alternatives to the use of animals in biomedical research and product safety testing. To date, the Center has funded some 300 grants (including renewals) for a total of more than $6 million. At its annual fall meeting, CAAT's Advisory Board members review applications to the research grant program, allowing members the opportunity to consider cutting-edge research and technology in the early stages. For 2008/9, CAAT awarded eleven grants relating to refinement, developmental toxicology,

immunotoxicology, and translational toxicology. The CAAT research grants program costs approximately $250,000 per year and is funded entirely through contributions from companies and foundations. The 2009/10 Call for Proposals is currently posted on the CAAT website.

CAAT's **Academic Programs** educate students and professionals in the research field about alternatives, helping them gain a better understanding of the 3Rs and their role in improving the quality of science. The Humane Science and Toxicology Certificate Program is central to CAAT's academic program, with a curriculum consisting of six courses, offered both in the classroom and on-line through the Johns Hopkins Bloomberg School of Public Health. The certificate program is open to anyone who holds an undergraduate or graduate degree in public health or the biomedical sciences, as well as to students in any degree-granting program at the Johns Hopkins University. In an important step designed to make the Certificate Program easily accessible to wide audience in business, legal and regulatory communities, CAAT is working to make the Humane Science and Toxicology Certificate Program available entirely on-line by 2010.

CAAT also offers a free online course: Enhancing Humane Science/Improving Animal Research. This course provides a broad overview of diverse topics in humane science, including experimental design, humane endpoints, environmental enrichment, post-surgical care, pain management, and the impact of stress on the quality of data. The self-paced course consists of 12 audio lectures with accompanying slides, resource lists, and study questions and is available on the CAAT website (http://caat.jhsph.edu/).

With the introduction of such EU regulations as REACH and the 7th Amendment to the Cosmetics Directive, EU-US relations in the field of humane science have become even more critical. CAAT is working to establish a Humane Sciences and In Vitro Alternatives component to a larger Johns Hopkins proposal for an **EU Center of Excellence**. In July, 2008, CAAT became part of the **American Consortium on European Studies** (ACES), in order to establish a Humane Sciences and In Vitro Alternatives component to this EU Center of Excellence based at the Johns Hopkins School of Advanced International Studies (SAIS). One of eleven EU Centers of Excellence in the United States, ACES (http://transatlantic.sais-jhu.edu/index.htm) was created in 2001 to advance academic and public understanding of the European Union and to improve US-EU relations. It seeks to strengthen education and research opportunities and to create new synergies among scholars, students, policymakers and the private sector, representatives of governmental and non-governmental organizations, and the media. In addition to SAIS, the Consortium includes American University, George Mason University, George Washington University, and Georgetown University.

Through ACES, CAAT will serve as an information gateway, working to establish programs that provide reciprocity in communication between the EU and the US in the area of alternatives and the humane sciences. As part of this EU Center of Excellence, CAAT will coordinate EU-related humane sciences and alternatives activities in the United States, share US progress with our European counterparts, and foster a greater understanding and awareness of alternatives and the respective regulatory requirements of the EU and the US.

CAAT will hold a **1-day workshop and information session for members of the cosmetics and personal care industry** on July 8, 2009 in Baltimore, Maryland. This session will offer an in-depth update on the 7th amendment of the European Cosmetics Directive, which went into effect on March 11, 2009, and bans the sale of any cosmetic product if either the finished product or any ingredients has been tested on animals. (The March 2013 deadline only applies to the following three test areas: reproductive toxicity, repeat dose toxicity and toxicokinetics.) If you register by July 1, 2009, this workshop is free for all CAAT sponsors and their employees, and $800 for others. After July 1st, the cost will be $200 and $1200, respectively. Registration is required.

In addition to the "Food for Thought" articles in ALTEX, the following **articles** may be of interest:

- Goldberg, A. and Hartung, T. (2008). The emerging new toxicology – an opportunity for contract research. *Eur. Pharmaceut. Contractor*, 42-46.
- Hartung, T. (2008). Towards a new toxicology – evolution or revolution? *ATLA 36*, 635-639.
- Hartung. T. (2009). A toxicology for the 21st century – mapping the road ahead. *ToxSci Advance Access* published on April 8, 2009. http://toxsci.oxfordjournals.org/cgi/reprint/kfp059

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USA/CAN/JAP/EU: Countries unite to reduce animal use

Representatives from four international agencies, including the director of the U.S. National Toxicology Program (NTP), signed a memorandum of cooperation that could reduce the number of animals required for consumer product safety testing worldwide. The agreement between the United States, Canada, Japan and the European Union will yield globally coordinated scientific recommendations on alternative toxicity testing methods that should speed their adoption in each of these countries, thus reducing the number of animals needed for product safety testing. The memorandum is available at http://iccvam.niehs.nih.gov/docs/about_docs/ICATM-MOC.pdf .

The agreement promotes enhanced international cooperation and coordination on the scientific validation of non-and reduced-animal toxicity testing methods. If the toxicity testing methods are shown to be reproducible based on strong scientific information, and able to accurately identify product related health hazards, the tests are more readily accepted by regulatory agencies.

Federal agencies are committed to the welfare of animals used in research. All animals used in federally-funded research are protected by laws, regulations and policies to ensure they are used in the smallest number possible and with the greatest commitment to their comfort. ICCVAM is working to promote the development and validation of alternative test methods.

The European Centre for the Validation of Alternative Methods coordinates validation studies on proposed alternative methods, evaluates the results by peer review, and provides recommendations to the European Union National Coordinators for regulatory acceptance of the methods validated. For more information on ECVAM, visit http://ecvam.jrc.it/.

The Japanese Centre for the Validation of Alternative Methods is a component of Japan's National Institute of Health Sciences and was established in 2005 to coordinate validation studies on proposed alternative methods, conduct peer reviews of test methods, and provide recommendations to regulatory authorities.

The Environmental Health Science and Research Bureau within Health Canada coordinates activities relevant to health-related test method validation and acceptance issues. For additional information, visit http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hecs-dgsesc/sep-psm/ehsrb-bsser-eng.php.

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) administers and provides scientific support for ICCVAM and is a part of the NTP at the NIEHS. For additional information, visit NICEATM at http://iccvam.niehs.nih.gov/about/about_NICEATM.htm.

NIEHS supports research to understand the effects of the environment on human health and is part of the National Institutes of Health (NIH). For more information on environmental health topics, visit our website at http://www.niehs.nih.gov.

NIH press release, April 27th 2009

Calendar of Events

» Forinvitox Forum event "From innovation to market success".
May 12-14, 2009,
Karolinska Institute Stockholm, Sweden.
Info: http://forinvitox.org/

» 19th Annual Meeting of the SETAC Europe – Society of Environmental Toxicology and Chemistry.
May 31-June 4, 2009,
Goeteborg, Sweden.
Info: http://goteborg.setac.eu/?contentid=13

» UFAW International Symposium 2009. Darwinian selection, selective breeding and the welfare of animals.
June 22-23, 2009,
University of Bristol, Bristol, UK.
Info: http://www.ufaw.org.uk/UFAW-SYMPOSIUM2009.php

» International course on Laboratory Animal Science – Utrecht, The Netherlands.
July 6-17, 2009,
Division of Laboratory Animal Science, Faculty of Veterinary Medicine.
Info: e-mail: las@uu.nl, www.vet.uu.nl/las>Education and Training>International course

» The 2009 International Academic and Community Conference on Animals and Society: Minding Animals.
July 13-18, 2009,
Civic Precinct, Newcastle, Australia.
Info: http://www.mindinganimals.com/

» 7th World Congress on Alternatives and the Use of Animals in Life Sciences.
August 30-September 3, 2009,
Rome, Italy.
Info: http://www.aimgroup.eu/2009/WC7/index.html

USA: Inauguration of the Doerenkamp-Zbinden Chair at Johns Hopkins University

Cheer for chair – some observations from the inauguration of Thomas Hartung as the Doerenkamp-Zbinden Chair for Evidence-based Toxicology

The Johns Hopkins University is a private research university in Baltimore, Maryland, United States. Johns Hopkins (named after Johns Hopkins, who left $7 million in his will 1873 – at the time, this was the largest philanthropic bequest in US history equivalent to $131 million in the year 2006) has graduate programs in medicine, public health, music, and international studies. Johns Hopkins is one of the top universities in the world – for example it ranked first of 20 top US academic institutions in total research & development spending for the 29th year in a row. And Johns Hopkins is known to entertain already for 28 years the Center for Alternatives to Animal Testing (CAAT), which became under the leadership of its founder Prof. Alan Goldberg a key promoter for alternative methods in the US, best known for its website AltWeb (http://altweb.jhsph.edu/) and the TestSmart workshops and conferences (last on developmental neurotoxicity in November 2008). It was not easy to find somebody to succeed Alan Goldberg, who turns 70 this fall: For more than four years, search committees looked for a candidate with a reputation and academic standing adequate for this prominent position.

Thomas Hartung fulfilled these criteria – a professor from the University of Konstanz, Germany, with more than 300 scientific papers and from 2002 to 2008 head of ECVAM, the European Center for the Validation of Alternative Methods. When asked what made him change to the US, his answer was quick: "The fantastic environment of Hopkins and the enthusiastic discussion on a paradigm shift in toxicology stirred by the vision report from the US National Academy of Sciences". The Doerenkamp-Zbinden Foundation enabled this change by endowing a chair for evidence-based toxicology linked to CAAT. On the basis of this endowment Hopkins commits to maintain a chair with this research direction until the university ceases to exist.

On 12th of May 2009, we were able to witness the celebration of the inauguration, which demonstrated impressively, how much the university embraces this donation and this area of research. University president Ron Daniels and Dean Michael Klag left no doubt about their full support, expressing their appreciation for the past of CAAT and their expectations for seeing it further flourish in the future.

In an entertaining presentation, Thomas Hartung laid out some stations of his career, which led him to Baltimore. As a thought starter, he recalled when he synthesized aspirin as a student of biochemistry and medicine in Tuebingen, Germany. Seeing the result of his work, he wondered whether he would dare to swallow it. Most probably not, if he would rely on to todate's toxicology, which has shown that the chemical is "harmful if swallowed", a skin, eye and respiratory irritant, a co-carcinogen and embryotoxic in cat, dog, rat, mouse and monkey. Good that there was no toxicology in 1899 – the drug would hardly have made it to the market. In marked contrast, after one million billions of pills taken by men, annual production is close to 50 thousand tons and sales close to $ 800 million. Hartung then showed, how his mentor Albrecht Wendel, Tuebingen and Konstanz, guided him toward pharmacology and toxicology, citing former FDA president Arnold Lehmann "You too can become a toxicologist in two easy lessons, each ten years long." He continued showing how the years in ECVAM with the European Commission have shaped his view on toxicology and the need for new approaches. The close collaboration with Alan Goldberg and CAAT during these years enabled a smooth transition now. Among others Hartung and Goldberg published in 2005 an article in Scientific American (later translated into Arabian, Chinese, German, Italian, Japanese, Korean, Polish, Portugese, Spanish and other) entitled "Protecting more than animals". This describes well their joint approach, which stresses that humane science is the best science – to protect consumers and patients as well as animals.

Finally, Hartung explained again his concept to translate Evidence-based Medicine to toxicology (see also his article in this issue of ALTEX). All together, an entertaining presentation, which set the scene for prospects in research, education and the "CAATalyst" role of the center.

The Doerenkamp-Zbinden foundation is proud to have helped install at such prominent place a chair to support the paradigm shift in toxicology. The choice of the inaugural professor raises hopes as to the contribution to be expected. By supporting the Transatlantic Think Tank of Toxicology (t^4) – a collaboration of the toxicology oriented Doerenkamp-Zbinden chairs in Konstanz, Utrecht and Baltimore – the support continues to make a new approach in toxicology possible. The photographs from the inauguration give an impression of the event – a milestone on the long road to go.

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The Baltimore ALTEX Office

Besides Thomas Hartung, now the Editor of ALTEX in the USA, two Baltimore staff members should be introduced to our readers.

Carol Howard

Carol Howard has been a science writer for more than 20 years and has worked at CAAT for the past 9 of those years. She is responsible for content development for a wide range of CAAT publications, including Altweb, the Alternatives to Animal Testing Website (http://altweb.jhsph.edu).

Carol holds a Master's degree in biology and a Bachelor's degree in psychology. She completed a one-year graduate program in science communication as well. She is author of the non-fiction book *Dolphin Chronicles* (Bantam Books, 1996). Her writing also has been published in National Geographic Books, Time Life Books, *Psychology Today, Reader's Digest*, and various literary journals.

A life-long love of animals and long-standing interest in science attracted Carol to CAAT and the field of alternatives. She is looking forward to working with ALTEX.

Michael Hughes

Michael Hughes has been a Communications Associate with CAAT since 2004, and has produced Web, video, and print content to further CAAT's mission of advancing humane science and promoting alternatives to animal testing. Over the past two decades he has worked in a variety of media, including Web, television, and print, as a writer, editor, designer, video producer, and photographer. He specializes in social networking, blogging, technology, and new media, and has published feature articles as well as short fiction. He lives in Baltimore, Maryland, with his wife and two daughters.