

INVESTIGATING ALTERNATIVES TO ANIMAL TESTING: ECETOC WORKSHOP REVIEWS TESTING METHODS FOR MUTAGENICITY AND GENOTOXICITY



The use of alternative testing strategies to reduce the use of animals is becoming increasingly important within the context of the new European chemicals legislation, REACH, and the 7th Amendment to the Cosmetics Directive. Alternative approaches have been proposed for some toxicological endpoints but others, such as that for mutagenicity or genotoxicity, still need to be developed for more widespread application.

The testing for mutagenicity and genotoxicity often gives rise to positive in vitro genetic toxicity results, which then require additional in vivo testing.

Several classes of materials such as chelating agents, heavy metals and some surfactants are not suitable for in vitro testing due to historic false positive results and/or incompatibility with in vitro test systems. In order to review the

possibilities of refining in vitro testing for mutagenicity and genotoxicity, Cefic LRI (Long-range research initiative) proposed a Workshop, which ECETOC organised this 23-24 April in Malta.

Some 40 invited scientific experts from industry, academia, and governmental agencies participated in the event which was begun with detailed presentations that lead into 5 breakout sessions and concluded with a plenary review of the working group's conclusions.



The workshop concluded that current in vitro testing methods were effective in detecting genotoxic carcinogens, albeit with some false positive findings. While current methods can detect genotoxic chemicals, they are relatively ineffective at detecting non-genotoxic carcinogens, so safety testing would benefit from introducing new methods. Emerging technologies and non-standard materials also require refined testing methods. Working groups evaluated new methods which use modified cells and human-specific metabolic activation systems. Furthermore, methodologies applying systems biology such as genomic technologies were considered. Related aspects were also raised including a better understanding of the role of population polymorphisms on susceptibility to carcinogens and the value of DNA-adduct biomarkers. The workshop identified areas where new improved methods are required and made some specific recommendations for future research on method development which are detailed in the full report.

To consult all recommendations, click [here](#) to download the report.

SG CORNER

It seems a very short time since the last newsletter, but six months have passed. Since that time, the new 'Science Strategy' has become our daily life at ECETOC and just last month we reviewed its content at the Scientific Committee. This has led to identification of priority areas for future task forces where we are not yet active. Over the next few months, the task force announcements will reflect this new approach. Over the same period, the website will be developed to make the link between the strategy and the task forces more obvious to our site visitors.

In the meantime, we have been very active since the AGM: five workshops have been organised and several new task forces were initiated.

Workshops

In June, we held a workshop on 'Biodegradation and Persistence' near Manchester. This event was co-sponsored by the Environment Agency for England and Wales and brought together experts from 10 European countries, plus the USA and Canada to discuss the problem of testing for biodegradability. The report has been published and can be downloaded from our website.

In September, we organised a workshop at the annual meeting of the European Environmental Mutagen Society in Basel. This is the 9th year we have had a workshop at the EEMS congress and we were again happy to be sponsored by CEFIC LRI to run this event. The subject of genotoxicity of nanoparticles attracted a large and lively audience.

In October we organised a workshop at the Eurotox congress called 'from a hazard- to a risk-based classification of carcinogens.' This was an opportunity to present the interim conclusions of our 'classification of carcinogens under GHS' task force on a platform which included speakers from US EPA, WHO and national authorities. Such was its popularity, we had to use a larger room than planned.

In November, we co-hosted a workshop with TNO on behalf of the European Commission on 'the use of human data for DNEL derivation.' This subject is of great importance in the implementation of REACH and capitalised on the expertise of our task force on the use of human data.

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SG CORNER continued..

Finally, in December we held a very timely workshop in Malaga to evaluate the use of the 'omics' technologies in human and environmental risk assessment. Speakers from chemical, pharmaceutical and consumer products companies shared case studies with regulators and academics from Europe and the USA.

New task forces

New task forces have been starting work at a tremendous pace. Since the AGM we started work on cardiac sensitisation methods, on triggering and waiving criteria for one-generation reproduction studies, on nanomaterials and OCED guidelines, and on potency values from the LLNA skin sensitisation study. At the same time we launched reviews of linear polydimethylsiloxanes, cyanide antidotes and the carcinogenicity of formaldehyde.

People news

All of this amounts to a busy time for the secretariat who have been a blur of activity organising all these activities. Luckily we have been able to fill two vacancies we had at the beginning of the summer. Anita Jennings joined us as a secretary and managed the logistics of the Malaga meeting, while Dr Malyka Galay-Burgos joined us from Cardiff University bringing expertise in environmental science and the omics technologies.

On the Scientific Committee we said "cheerio" to Geoff Randall after several years in the chair and welcomed John Doe to that role. Meanwhile, the departure of Tom Hutchinson and Mike Comber from their companies has resulted in the loss of great experience in environmental sciences on the Scientific Committee. We are currently seeking new candidates as we have a full and exciting portfolio of activities in this area.

Seasons greetings

So, my first year behind the wheel has been full of changes of personnel and activities. It has been a lot of fun and I hope those of you who have participated in one of our activities have also enjoyed it. All of us here wish you a great festive season and hope that "Santa" is generous to you. We look forward to your support and partnership in 2008.

Neil Carmichael

Dr. Neil Carmichael
Secretary General



ouTReACH France



In mid-September, ECETOC was happy to accept the hospitality of DuPont to run its first French OutREACH event in Paris.

Their offices in Paris La Defence proved an excellent setting for ECETOC to showcase its activities.

The Secretary General presented an overview of the science strategy to French based companies, both members and non-members. Several regulatory agencies and research institutes were also represented. The strategy was then illustrated by several members of the scientific committee and taskforce chairmen who presented the activities of the current task forces. An excellent buffet lunch allowed for a free flowing discussion and an excellent informal networking opportunity. Everyone seemed to enjoy the occasion and thanks are due to the DuPont Paris staff and to ECETOC members for their efficient and impeccable support.

ECETOC YOUNG SCIENTIST Awards 2007

Each year, ECETOC sponsors three awards for young scientists and is proud to announce this year's winners:

For the **environmental science related award**, the ECETOC Young Scientist Award at the Society of Environmental Toxicology and Chemistry (SETAC) Europe Annual Congress (Porto, Portugal, 20-24 May 2007) went to:

Mr. Thijs van Boxtel of the Vrije Universiteit Amsterdam his platform presentation, entitled 'Mechanisms of toxicity of polybrominated phenoxyphenols and anisols of natural and anthropogenic origin in the zebra fish.'

For the **human health related science award**, the ECETOC Young Scientist Award at the European Societies of Toxicology (EUROTOX) Annual Congress (Amsterdam, The Netherlands, 7-10 October 2007) was split between two researchers who had worked together on their posters entitled 'Aging influences segment-specific toxicity of the proximal tubule caused by chemicals. I. Histopathological and biochemical findings' by Rossella Defazio et al., and 'II. Gene expression in kidney tissue' by Arianna Chiusolo et al., both from GlaxoSmithKline, Verona, and the Department of Environmental Medicine and Public Health, University of Padova, Italy.

For the first time in 2007, ECETOC sponsored a **young scientist award for epidemiology related science** in association with the International Commission on Occupational Health's Scientific Committee on Epidemiology in Occupational Health (EPICOH). On the occasion of their Annual Congress (Banf, Canada, 9-12 October 2007) this was awarded to Jennifer Cavallari, Department of Environmental Health, Harvard School for Public Health, for her poster titled 'Circadian variation of heart rate variability following metal-rich fine particle exposures in boiler maker construction workers.'

The winners have been encouraged to use the awarded prizes for the advancement of their careers.



ECETOC contributes to EEMS congress for 9th year in a row

For the 9th year in a row, an ECETOC task force came together to prepare a symposium for the annual general meeting of EEMS, the European Environmental Mutagen Society. Held on Tuesday 11 September in Basel, this year's symposium was entitled 'toxicology/genotoxicity of manufactured nanoparticles' and sought to present new data from on-going industry/academic projects on genotoxicity and draw attention to related relevant aspects such as characterisation, exposure, transportation, mode of action and immuno-translocation. The programme included presentations on these aspects plus the results of genotoxicity testing of typical nanoparticles (TiO₂ and ZnO) and newly engineered nanofibres (nanotubes).

The symposium was attended by over 200 (out of a total of 350) conference participants and the audience, including many key scientists, showed a high interest in this new topic.

In his conclusions, ECETOC Secretary General, Neil Carmichael highlighted the stability of the test system and specific dosimetry as major challenges for nanoparticle investigations. Earlier, studies often lacked sufficient characterisation of the test material or lacked appropriate control groups, i.e. in the absence of micro-particle treated groups, it is impossible to decide whether nanoparticle-mediated adverse effects are intrinsic to the test material or specific for particle size. Even in present studies, a change of conditions might alter the results and influence the conclusions, especially in *in vitro* models. Material reaching the tissue might have different characteristics, e.g. in case of intratracheal instillation. So far, there were few reports of direct genotoxic effects of nanoparticles. Indirect genotoxicity mediated by toxicity might allow for the derivation of thresholds. In all, to be useful for risk assessment, the model system had to be well characterised and representative of the conditions of exposure.

LATEST Publications



ECETOC is proud to report the publication of its largest report to-date.

The **Cyanides of Hydrogen, Sodium and Potassium, and Acetone**

Cyanohydrin was published this September after months of dedicated efforts by task force members. This two-volume publication is the definitive reference for the WHO and poison centres alike.

An ECETOC task force on cyanides antidotes has just been launched this summer.

JACC 53 Vol I and II

Cyanides of Hydrogen, Sodium and Potassium, and Acetone Cyanohydrin (CAS No. 74-90-8, 143-33-9, 151-50-8, 75-86-5), published September 2007

Workshop Report 9

Refinement of Mutagenicity/Genotoxicity Testing, 23-24 April 2007, Malta, published September 2007

Workshop Report 10

Biodegradation and Persistence, 26-27 June 2007, Holmes Chapel, United Kingdom, published September 2007

ECETOC In Brief

ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals, was established in 1978 as a scientific, non-profit, non-commercial association, financed by 52 of the leading companies with interests in the manufacture and use of chemicals. A stand-alone organisation, it was established to provide a scientific forum through which the extensive specialist expertise in the European chemical industry could be harnessed to research, review, assess and publish studies on the ecotoxicology and toxicology of chemicals.

Website

Be sure to visit www.ecetoc.org to download any of our [publications](#)

FORTHCOMING Meetings

January

- 11 Guidance for the classification of carcinogens under GHS task force meeting
ECETOC Offices, Brussels
- 21-22 Nanomaterials and OECD test guidelines task force meeting
ECETOC Offices, Brussels
- 29-30 Assessment and management of dermal risks from industrial chemicals task force meeting
ECETOC Offices, Brussels
- 31 Scientific Committee meeting
ECETOC Offices, Brussels

February

- 5 Mixtures task force meeting
ECETOC Offices, Brussels
- 12 Potency values from the LLNA: Application to classification, labelling and risk assessment task force meeting
ECETOC Offices, Brussels
- 21-22 Biodegradation kinetics task force meeting
ECETOC Offices, Brussels

April

- 1-2 Scientific Committee meeting
ECETOC Offices, Brussels
- 14-15 Triggering and waiving criteria for the extended one-generation reprotoxicity study workshop (by invitation only)
ISPRA, Italy
- 17 Long Range Research Initiative (LRI) Health Effects Monitoring Team (HEMT) meeting
ECETOC Offices, Brussels

- 18 Potency values from the LLNA: Application to classification, labelling and risk assessment task force meeting
Bayer Wuppertal, Germany

June

- 3 Scientific Committee meeting
ECETOC Offices, Brussels
- 4 Annual Technical Meeting (ATM)
Martin's Central Park Hotel, Brussels
- 5 Board meeting (10.00-13.00)
Martin's Central Park Hotel, Brussels
- 5 Annual General Meeting (AGM) (13.00-15.30)
Martin's Central Park Hotel, Brussels

Next Edition ...

Look out for a report on ECETOC's recent Omics Workshop.

EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

Av. E. Van Nieuwenhuyse 4 (Bte) 6 B-1160 Brussels, Belgium

Tel: +32 2 675 3600 Fax: +32 2 675 3625 VAT: BE 041834469

For more information about ECETOC and/or the content of this e-newsletter, please contact us info@ecetoc.org