

KEY ELEMENTS OF THE FUTURE OECD TEST GUIDELINE FOR AN EXTENDED ONE-GENERATION REPRODUCTION TOXICITY STUDY ADDRESSED BY ECETOC WORKSHOP



Strategic Science Area:
Intelligent Testing Strategies

Under the chemicals legislation in Europe: REACH, the two-generation reproductive toxicity study, OECD TG 416, will be a key component for the risk assessment of chemicals. It is a default requirement for substances produced or imported at >1000 tonnes per annum. This is a complex study that involves a large number of animals, takes nine months from start of treatment to necropsy, and is costly.

In 2006, a proposal was made by the Agricultural Chemical Safety Assessment (ACSA) technical committee of ILSI HESI for an extended one-generation study design that is composed of several components: second breeding for an F₂ generation, developmental neurotoxicity and developmental immunotoxicity.

The reduction in animal usage when substituting the guideline two-generation study with an extended one-generation study design is substantial. A two-generation study conducted to OECD TG 416 will entail the use of approximately 2600 animals. If a standalone developmental neurotoxicity study is also conducted, this will add at least 1200 animals, bringing the total to around 4000. An appropriately designed extended one-generation study would use around 1400 animals or 2600 if a second breeding is triggered.

Also in 2006, two workshops held by ECVAM (European Centre for the Validation of Alternative Methods) and the EPAA (European Partnership for Alternative Approaches to Animal Testing) discussed the ACSA proposal in detail and agreed that the extended one-generation study could, in principle, be applicable to safety testing under REACH. However, it was also agreed that the complex protocol should be modified in order to meet the current requirements for industrial chemical safety testing.

An ECETOC/ECVAM task force has built on this proposal and developed triggering and waiving criteria for the modules of the extended one-generation reproduction toxicity study. These are proposed for deciding on the study design addressing a chemical's reproduction toxicity potential in a tiered testing strategy. Validation criteria for the triggers and waivers have also been proposed. In order to review and discuss the concepts with a multi-stakeholder group, an ECETOC workshop was held 14-15 April 2008 in Barza d'Ispra organised in collaboration with ECVAM and co-sponsored by Cefic-LRI. Chaired by Dr. Nigel Moore (of Dow Europe and chairman of the related ECETOC/ECVAM task force), 40 participants from regulatory agencies, academia and industry reached common positions for the triggers and waivers of the study modules.

The conclusions have been summarised by the task force and are published as ECETOC Workshop Report No. 12. This has been submitted to the OECD expert group on the guideline for the extended one-generation reproduction toxicity study (who were also represented at the workshop) in advance of their next meeting in October 2008.

SG CORNER

The summer got off to a warm start for the staff of ECETOC; the month of June was a blur of activity. Not only were there Board and Scientific Committee meetings, but we held the Annual General Meeting (AGM), the Annual Technical Meeting (ATM) and two scientific workshops. The AGM and ATM were held at the Martin's hotel in the EU district where our first challenge was to get past the protesting fishermen and riot police with associated barricades, closed streets etc. In the end everything went smoothly enough!

The AGM of course, is the primary opportunity of the year for members to see how the association is developing its activities and using its resources. The past year's finances are presented and the coming year's budget is submitted for approval. It is the moment for the participants to give their input as to the way the association is addressing the needs of the membership. I would like to encourage more companies to participate and give feedback at this annual event.

The Chairman's speech concentrated on the activities of ECETOC in the context of REACH implementation. Dr Jochen Rudolph highlighted several activities which will have practical impact as the regulation is applied. For example, the ECETOC workshop on derivation of DNEL's (referred to elsewhere in this newsletter) and ECETOC's Targeted Risk Assessment tool are inputs which will make a real difference.

Dr Rudolph also highlighted the shifting demographics of the ECETOC membership. Many of the senior experts are approaching retirement and will take a huge fund of experience with them. ECETOC is therefore actively encouraging the participation of younger scientists in its activities. This will give them the opportunity to work alongside and learn from scientists with decades of practical experience. In order to further promote this objective, ECETOC will organise a specific event for the benefit of younger scientists. The next newsletter will announce details of this.

Succession loomed large at the AGM itself: three board members retired from their companies and two retired from the board at

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SG CORNER continued..

the same time. Mr David Gartside from Astra Zeneca and Dr Charles Murray both resigned and the Chairman thanked them for their years of enthusiastic participation and wisdom that they contributed. Dr Rudolph himself was retiring from Evonik-Degussa, but had graciously accepted to remain as Chairman of the Board of ECETOC for one more year.

At the same time, we welcomed three new members to the board: Dr Julia Fentem of Unilever, Dr Hans Bender of Proctor & Gamble and Mr Steve Rumford of Astra Zeneca. Twelve months from now, there will only be one board member who was on the board when I came to ECETOC in 2006.

Of the June workshops, the meeting in Oslo is detailed later on in this newsletter. The other, which was held in Brussels, addressed the possibility of using the latest analytical techniques to quantify past exposure to chemicals. These 'retrospective biomarkers' could potentially include changes in cell proteins, nucleic acids, lipids etc. The workshop was sponsored by the European Crop Protection Association (ECPA) and brought together leading experts from all over Europe. As you can see, from the forthcoming meetings box, this autumn is busy too. We will be running sessions and workshops at international conferences in Croatia and Greece.

Finally, as I referred earlier to decades of experience, we shouldn't forget to mention a member of the Secretariat who has accumulated a grand two decades of experience here, involvement in some 30 task forces, over 40 reports and quite a few publications: Ir. Henk Vrijhof has been working as a scientist here since 1988 and has seen three Secretary Generals come and go before me.

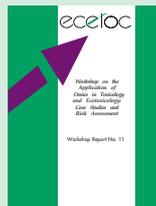
Last but not least, ECETOC itself will be 30 years old this year, but more of that in the next newsletter!

Neil Carmichael

Dr. Neil Carmichael
Secretary General

LATEST Publications

Workshop on the Application of 'Omics in Toxicology and Ecotoxicology:



Case Studies and Risk Assessment

Workshop Report No. 11

Published July 2008

Difluoromethane (HFC-32) CAS No. 75-10-5

(Second Edition)

JACC Report No. 54

Published June 2008



ECETOC 2008 ANNUAL TECHNICAL MEETING

COUNTING THE COSTS AND BENEFITS OF CHEMICAL CONTROL:

THE ROLE OF ENVIRONMENTAL RISK ASSESSMENT IN SOCIO-ECONOMIC ANALYSIS



Strategic Science Area:
Science in society

The ECETOC 2008 Annual Technical Meeting was organised this 6 June in Brussels as another 'Futures Workshop' to contribute to our strategic science area 'science in society'.

The topics, cost-benefit/socio-economic analysis (CBA/SEA), were selected because they are anticipated for the implementation of REACH as well requirements in the EU water and environmental liability legislation. Therefore in organising this workshop, ECETOC has been helping industry to build understanding and expertise in these areas.

In line with ECETOC's remit to develop the best possible science for the risk assessment of chemicals, the workshop participants were asked to evaluate whether and how we can contribute to defining the role of environmental risk assessment in CBA/SEA. Under the chair of Prof. Calow from ECETOC's Scientific Committee, seven high profile

speakers from the natural and economic sciences provided the background and latest developments. This was followed by break-out group discussions.

In all, the workshop recommendations are that ECETOC can play a role, and five themes evolved for potential actions, namely:

- appropriately quantifying changes in impact associated with proposed risk reduction strategies;
- informing the process of valuation by enabling collaborations between natural scientists and economists;
- supporting the process of socio-economic analysis, for example by facilitating multi-disciplinary team building;
- developing one or more exemplary case studies;
- playing an active role in cross-disciplinary networking and capacity building.

The full outcome of the workshop will soon be published as an ECETOC Workshop Report No.13.

ECETOC CO-ORGANISES WORKSHOP WITH EUROPEAN COMMISSION AND TNO ON USE OF HUMAN DATA FOR DNEL DERIVATION



Strategic Science Area:
Risk, hazard and precaution

During the drafting of the initial European Technical Guidance on Information Requirements and Chemical Safety Assessment (IR&CSA) on how DNELs (derived no-effect level) and DMELs (derived minimal effect level) should be derived under REACH, only animal studies were referred to. Although the draft IR&CSA Technical Guidance Documents (TGD) recognised the value that human data provide in interpreting the nature of health effects, no guidance was offered on how they should be used for setting the DNELs and DMELs. ECETOC therefore raised the issue as part of its comments to the stakeholder review process for the IR&CSA TGD. The Stakeholder Expert Group (SEG) agreed with ECETOC's suggestion that there was a need for further guidance to be developed. With the support of the European Commission, ECETOC and TNO organised a workshop in Brussels to address this issue, last 20 November 2007.

Using the emerging thoughts of an ECETOC Task Force on 'Framework for the Integration of Human and Animal Data in Chemical Risk Assessment' as a key input, a discussion document was developed in advance of the Workshop. This proposed a process by which available human data could be evaluated regarding their quality and relevance and then, in combination with available animal findings, be used to derive DNELs and DMELs in a manner consistent with that preferred by the European Commission (i.e. assignment of assessment factors, the magnitude of which is influenced by the uncertainty of the supporting data).

Key conclusions of the event were that:

- the processes by which human data are evaluated for their relevance in DNEL/DMEL derivation should not be undertaken in isolation from that being carried out for available animal findings. The two forms of data were complementary; available animal data helped to inform the nature of the relevance of human findings and vice versa.
- the process for DNEL/DMEL derivation should be driven by the form of data (whether animal or human) that are

considered best for the particular DNEL (short or long-term) or DMEL. Where both human and animal data of equivalent quality are available then the human data should be given more weight.

- while the TGD addresses many factors that affect human data quality, it inadequately addresses how its quality (in terms of how the range of different study types and the reliability of these for particular questions) should be described. In this respect, the ongoing ECETOC activity in this area largely addresses this need.
- the REACH Technical Guidance needs a 'road map' which would aid non-experts to better understand the key elements of and the process for evaluating human data and to direct users to relevant sections of the TGD.

EChA (European Chemicals Agency) have requested that ECETOC continue to work with TNO to develop a text to address these points in order that they can be incorporated into a future revision to the IR&CSA TGD (anticipated for end 2008).

OSLO WORKSHOP LOOKS AT PROBABILISTIC MARINE HAZARD ASSESSMENT

In order to discuss the potential use of probabilistic techniques in marine environmental hazard assessment, a workshop was organised by ECETOC together with the Environment Agency for England and Wales on 18-19 June 2008.

Nearly 40 scientific experts from industry, academia and European governmental agencies participated in the meeting that was hosted by the Norwegian Pollution Control Authority and held in Oslo. Seven plenary sessions were followed by four syndicate sessions which concluded that the probabilistic approach is beginning to be applied for marine (and fresh-water) procedures and guidelines worldwide. However, some questions still remain and are related to the combination of data from marine and fresh water, extrapolation from one climatic zone to another, segregation of data by groups (fish versus invertebrates) and the combination of data based on different endpoints.

The next steps include the publication of an ECETOC workshop report and a paper in the open literature for which some of the speakers will be asked to collaborate.

The workshop recommendations are expected to stimulate scientific research and specific task force work at ECETOC. The workshop also proposed the joining organisation of a Symposium by ERASM (Environmental and Risk Management) and ECETOC for spring 2009, as a basis for the formation of a marine sediment task force.



Strategic Science Area: Biodiversity and ecosystems



Strategic Science Area: Intelligent Testing Strategies



Strategic Science Area: Risk, hazard & precaution

BRAINSTORMING MEETING IDENTIFIES SUBJECTS FOR NEW ECETOC TASK FORCES

Due to the argued inadequacies of current risk assessment methodologies, several regulations (e.g. POPs (persistent organic pollutants), REACH) do not allow or limit possibilities to conduct risk assessments as a basis for chemical management decisions. Instead, decisions are based on a strict interpretation of the precautionary principle leading to hazard (rather than risk) based restrictions.

In April 2008, a meeting was held to highlight further actions that ECETOC could take to advance the scientific basis for chemical risk assessment – particularly for those that are officially recognised as PBT (persistent, bioaccumulative and toxic), vPvB (very persistent very bioaccumulative) or POP (persistent organic pollutants).

During this 2-day meeting, 38 industry and academic participants addressed both environmental and human health concerns of assessing PBT chemicals and agreed a range of areas where an ECETOC task force could resolve specific risk assessment issues.

The areas identified were:

- The linking of biomonitoring results with effect levels for risk assessment of PBT chemicals of biomonitoring in the risk assessment;
- The application of CBB (critical body burdens) in risk assessment of SVHC (substances of very high concern);
- The assessment of metabolism in understanding the fate and effects of chemicals;
- A systematic analysis of literature on existing scientific and regulatory risk assessment approaches for PBT/vPvBs and POPs and preparation of a scheme of recommended approaches;
- Probabilistic risk assessment for SVHC.

The participants also identified a need for research to fill the knowledge gaps in fate and effect of chemicals in soil and sediment compartments.

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

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 51 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.

FORTHCOMING Meetings

September

- 16 Potency values from the LLNA: Application to classification, labelling and risk assessment task force meeting
- 22 Board of administration meeting ECETOC offices, Brussels
- 22 or 26 (tbc) Targeted risk assessment integration group meeting Cefic or ECETOC offices, Brussels
- 23 Scientific Committee meeting ECETOC offices, Brussels
- 25 Thresholds for genotoxins and their application in risk assessment symposium During EEMS Annual Meeting Cavtat, Croatia
- 25-26 The biological significance of DNA adducts: Part II workshop Post-EEMS Annual Meeting Cavtat, Croatia
- 30 Interpreting endocrine disrupting effects task force meeting Jealott's Hill, UK

October

- 7 Intelligent testing strategies: Current status and the way forward symposium
- 8 The role of science in society and industry sponsorship of environmental and health research symposium During EUROTOX Annual Meeting Rhodes, Greece
- 16 Targeted risk assessment full task force meeting
- 17 Targeted risk assessment environment group meeting
- 22-23 Scoping meeting on ecological risk assessment of mixtures in the environment Tbc, Brussels

November

- 13 Cyanide Antidotes task force meeting Frankfurt, Germany
- 18-19 Scientific Committee meeting ECETOC offices, Brussels
- 27-28 Interpreting endocrine disrupting effects task force meeting Tbc, France

Next Edition ...

We'll be feeding back on the two symposia being organised by ECETOC at this year's Eurotox Annual Meeting.

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