



ECETOC PUBLISHES ITS 'GUIDANCE ON ASSESSMENT FACTORS TO DERIVE A DNEL'

*Science Area:
Risk, hazard
and precaution*

The chemical industry has reached an important milestone this month by having submitted their dossiers for the first REACH registration deadline. This was also a significant timeline for ECETOC to observe as the report on 'Guidance on Assessment Factors to Derive a DNEL' had to be published by then. Companies were already referring to the tables on assessment factors communicated with the draft report this March, i.e. in preparation for the Workshop in Ispra/Italy where we discussed the underlying principles with regulators, academia and experts from industry. Since then, the ECETOC Task Force has worked diligently to address the helpful comments made at the Workshop. This required, for example, evaluating many original data from toxicological studies on industrial chemicals reported in the open literature. The guidance has now been published as Technical Report No. 110 (available at <http://bit.ly/ecetoc-tr110>).

TR 110 addresses the (human health) assessment factors for setting a DNEL. In the REACH Technical Guidance Document, chapter R.8 'Characterisation of dose[concentration]-response for human health' proposes a tiered and systematic approach for the delineation of DNEL (and DMEL). This approach is supported by ECETOC in principle, but it appeared advisable to provide additional scientific arguments and recommendations for the derivation of DNEL (to note: DMEL were not addressed). The Task Force that had started its work in mid-2009 critically assessed the approaches laid out in the REACH TGD, re-visited the previously published guidance on assessment factors (TR 86) and supplemented this with an updated review of the literature published on this topic during the intervening years. Although for most chemicals a DNEL will solely be based upon animal data, for some health effects data derived in humans will be an additional and important source of information. Hence, the conclusions from TR 104, providing a guide for an integrative framework for human and animal data, have also been referred to in TR 110.

ECETOC, in line with the R.8 guidance, recognise that the use of 'informed' assessment factors is preferred over 'default' assessment factors wherever possible, whether supported by substance-specific data or, for example, by read-across to other chemicals or mechanisms of action. The use of informed assessment factors for hazard and risk assessment is well-established and has been used for many years by organisations such as the Scientific Committee on Occupational Exposure Limits (SCOEL) and national competent authorities to set occupational exposure limits. The guidance in TR 110 is illustrated by a number of case studies drawn from, for example, SCOEL documentation, for which the outcome of assessments based on default (REACH TGD, chapter R.8) versus ECETOC recommended assessment factors has been compared.



SG CORNER

The annual meetings cycle is a year round activity at ECETOC; no sooner is one behind us than we start work on another. You may recall that the 2010 ATM and AGM were held on the same day in an experiment to try to maximise participation. We polled our participants shortly after and were reassured to find that this was a popular format, so we will repeat this in 2011. The Board has chosen the date, which you should already put in your diary: it will be 8th of June. The intention is to have an ATM which will be a showcase for ECETOC Task Forces. More details will be provided in the next e-newsletter.

In the meantime, we are working hard on the output of the last ATM. The 2010 ATM was a general review of ECETOC's strategy, including the science strategy. Since then the ideas which the meeting produced have been developed by the Board and the Scientific Committee. These include new ways of using the scientific resources at ECETOC's disposal and ways to increase added value for members. By the time of the next e-newsletter these should be concrete proposals.

In the shorter term, the science strategy was reviewed. The Strategic Science Areas concept has served us well and provided a focus for the Scientific Committee. It has allowed us to monitor the balance of our portfolio of activities and to ensure that areas which were identified as strategic were receiving sufficient attention. After three years in operation it was felt useful to reassess whether these SSA's were still appropriate.

Accordingly an exercise was performed at the ATM and later (independently) by the Scientific Committee to evaluate the importance of these 13 SSA's. The participants were asked to rank the SSA's in terms of the effort and impact that ECETOC had achieved with these activities. To illustrate, the chart of the analysis by the Scientific Committee is shown in figure 1. This is similar, but not identical, to the conclusions from the ATM; the conclusions are drawn from both. As a result of this analysis, the following decisions were adopted:

1. Sensitive sub-populations will no longer be a separate SSA as it is considered that the area where ECETOC has been most involved, children's health, is covered under reproductive health.
2. Indoor air should also no longer be an SSA as we are unable to define clear activities for Task Forces. (The report that we commissioned on childhood asthma is now published).

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Figure 1: SC RANKING OF SSAs Current Use / Influence



View larger image at http://bit.ly/ecetoc-en18-ssa_review

SG Corner continued..

3. There was only one SSA under the theme 'Chemicals in the Environment' i.e. 'exposure pathways', which was too broad and not sufficiently explicit. This will be split into two SSAs covering different aspects of fate and behaviour of chemicals in the environment.

4. The SSA 'omics should be merged into testing strategies, as it is now becoming integrated into more mainstream toxicology research, if not yet into any testing requirements.

5. The two SSA's entitled 'Biodiversity and Ecosystems' and 'Science in Society' were considered important, but the ideas behind them were insufficiently concrete for them to be readily understood by the membership. Further work will be required to give substance to these concepts.

In addition to the SSA's, we are working on tools for prioritising our activities to maximise the impact of the Task Forces or Workshops that we launch. The Scientific Committee is now working on these revisions and the new look Science Strategy will be published on our website early in the new-year. While on the subject of new-year; I take this opportunity to wish all our readers a happy festive season. As many of you will know, we made the decision two years ago to use the money previously spent on Christmas cards to make a donation to a local charity. Many of you who visit Brussels will have noticed that there are increasing numbers of homeless here, and we feel sure you will agree this donation on your behalf is a worthwhile gesture.



Dr. Neil Carmichael
Secretary General



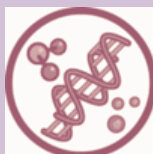
SCIENTIFIC COMMITTEE NEWS

Meeting with INERIS

In return for a visit of the Secretary General to INERIS (French Institut National de L'Environnement Industriel et des Risques) during last year, Dr P. Hubert, director of the Chronic Risk Division of INERIS, had been invited to meet with the Scientific Committee to share areas of common interest. INERIS is a French public research organisation, under the auspices of the French Ministry for Ecology, Sustainable Development and Spatial Planning. ECETOC previously co-operated with researchers from INERIS in the FP5 project Acutex that developed the Technical Guidance Document for the implementation of the so-called Seveso II Directive (emergency and land-use planning in case of major industrial accidents). Since then, we kept contact with INERIS and have frequently invited their experts to ECETOC Workshops.

Dr Hubert gave an overview on the activities of INERIS and, in particular, presented the research portfolio of his division. This includes topics like nanomaterials, alternatives (INERIS is the French platform of ECOPA), ecotoxicology and environmental modelling, as well as socio-economic analysis. Hence, there are a number of areas - in common with ECETOC activities that fit into our strategic science areas. Both the Scientific Committee and Dr Hubert expressed interest in co-operation between the two organisations where opportunities arise.

Dr. Fraser Lewis
Scientific Committee Chairman



Science Area:
'Omics'
and related
technologies

ECETOC AND EEMS HOLD SYMPOSIUM ON 'OMICS IN SYSTEMS BIOLOGY

ECETOC and EEMS (European Environmental Mutagen Society) have jointly organised a symposium entitled "Use of 'omics to elucidate mechanism of action and integration of 'omics in a systems biology concept". The symposium was co-funded by CEFIC-LRI and held on 16 September 2010 as part of the annual meeting of EEMS in Oslo.

The organisation of regular symposia has allowed ECETOC and EEMS to continue a successful relationship for more than 10 years. The papers of these symposia form critical state-of-the-science reviews; they have been published in the open literature.

This year's symposium in Oslo consisted of the following topics and speakers: Welcome – Neil Carmichael, ECETOC; Liver toxicogenomics within the pharmaceutical industry: From in vivo, to slice, to permanent cell line – Willem Schoonen, MSD; Sources of variation in baseline gene expression levels from toxicogenomics study control animals – Chris Corton, US EPA; Metabolomics, a tool for early identification of toxicological effects and an opportunity for biologically based chemical grouping under REACH – Bennard van Ravenzwaay, BASF; Toxicogenomics for genotoxicity and carcinogenicity prediction: The role of microRNA – Joost van Delft, University of Maastricht; Prediction in the face of uncertainty: A Monte Carlo strategy for systems biology of cancer treatment – Christoph Wierling, Max Planck Institute for Molecular Genetics; and Closing remarks – Bennard van Ravenzwaay, BASF. The whole session including debate after each presentation was attended by up to 200 persons. It was chaired by Jos Kleinjans, University of Maastricht and Gunnar Brunborg, Norwegian Institute of Public Health.

The above-mentioned speakers are a selected group of scientists who had made similar presentations at the ECETOC Workshop on the "Use of 'omics in (eco) toxicology: Case studies and risk assessment" held in Málaga in February 2010 (Workshop Report 19, available at <http://bit.ly/ecetoc-wr19>). The conclusions of the symposium in Oslo are fully in line with those made at the Málaga ECETOC Workshop. Both events built on an earlier ECETOC Workshop in 2007; "Application of 'omic technologies in toxicology and ecotoxicology" (Workshop Report 11, available at <http://bit.ly/ecetoc-wr11>).

The conclusions of the recent Oslo symposium (based on the previous ECETOC Workshops) can be summarised as follows:

'Omics sciences are taking their place among other hazard and risk assessment tools and are particularly valuable for understanding modes of action.

'Omics sciences add value to risk assessment by improving mechanistic understanding and identifying modes of action. However, 'Omics sciences at this time cannot be used for quantitative risk assessments – transcriptomics may be more sensitive than classical toxicology, whereas metabolomics appears to be equally sensitive. Alterations in individual parameters in 'omics studies are unsuitable to derive NOAELs. 'Omics NOAELs should be based only on specific patterns of change for potentially relevant biological effects, causally related to an adverse effect.

Specific patterns of change obtained in 'omics studies are being developed and used for the early identification of toxicological modes of action in the screening for novel compounds.

These technologies can potentially serve as a tool for prioritisation of chemical testing and could provide a better (biology-based) rationale for chemical grouping under the REACH legislation.

Good quality study design and data are essential to improve the confidence level and increase the likelihood of regulatory acceptance.



ARTICLE PUBLISHED IN THE OPEN LITERATURE ON 'SCIENCE BASED GUIDANCE FOR THE ASSESSMENT OF ENDOCRINE DISRUPTING PROPERTIES OF CHEMICALS'

Science area:
Reproductive health

+

Risk, hazard and precaution

Building on the findings of the 2008 Task Force and 2009 Workshop on identifying endocrine disrupting effects, an article is now being published in *Regulatory Toxicology and Pharmacology* that presents refined guidance and addresses some key considerations raised by the regulatory, academic and industry scientists who attended the Workshop.

Background

The European legislation on plant protection products (Regulation (EC) No. 1107/2009) and biocides (Directive 98/8/EC), as well as the regulation concerning chemicals (Regulation (EC) No. 1907/2006 'REACH') only support the marketing and use of chemical products on the basis that they do not induce endocrine disruption in humans or non-target species. However, there is currently no agreed guidance on how to identify and evaluate endocrine activity and disruption. Consequently, an ECETOC Task Force was formed in 2008 to provide scientific criteria that may be used within the context of these three legislative documents.

The report created by the Task Force (Technical Report 106, June 2009) reviews and summarises existing definitions of an endocrine disrupter as well as the test methods currently available to identify endocrine activity and/or toxicity. Specific scientific criteria for the determination of endocrine disrupting properties that integrate information from both regulatory (eco)toxicity studies and mechanistic/screening studies are proposed. These scientific criteria rely upon the nature of the adverse effects detected in regulatory (eco)toxicity study(ies) that give concern for endocrine toxicity and the description/understanding of the mode of action of toxicity which scientifically support and explain the adverse effects. The criteria developed are presented in the form of flow charts for assessing relevant effects for both human and environmental species (see figures 1, 2 and 3 below). These charts are illustrated using example substances. In addition since all chemicals having endocrine disrupting properties may not represent the same hazard, an element or assessment of potency is also proposed to discriminate chemicals of higher concern from those of lower concern.

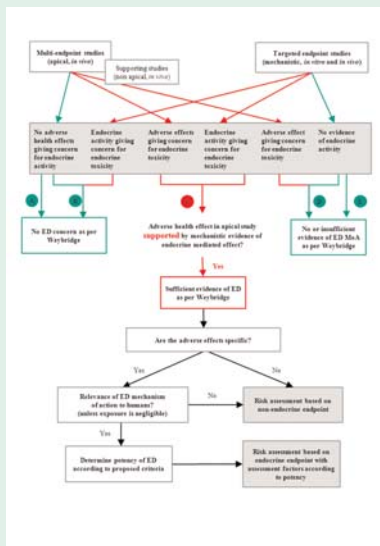


Figure 1: View larger image at <http://bit.ly/ecetoc-en18-endocrine01>

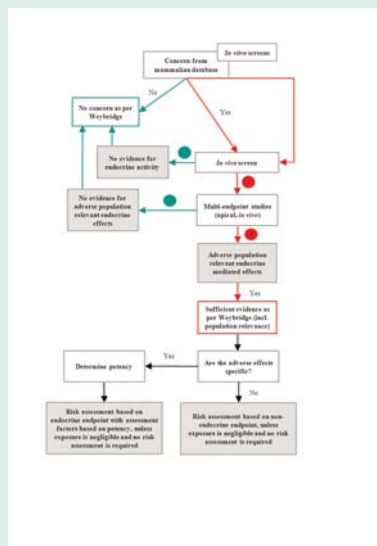


Figure 2: View larger image at <http://bit.ly/ecetoc-en18-endocrine02>

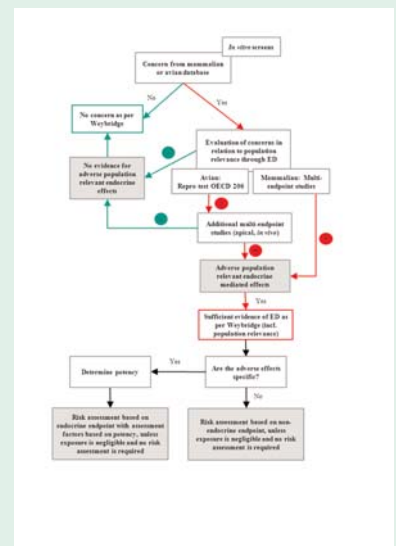


Figure 3: View larger image at <http://bit.ly/ecetoc-en18-endocrine03>

ECETOC presented this proposal (Technical Report 106¹) at a Workshop of regulatory, academic and industry scientists (Barcelona; June 29-30, 2009) to evaluate the approach as a concept for identifying endocrine disrupting properties within a regulatory context. The outcome of this Workshop has been published in a separate report (Workshop Report 16 and Addendum²).

Article:

Bars, R., et al. Science based guidance for the assessment of endocrine disrupting properties of chemicals. *Regul.Toxicol.Pharmacol.*(2010), doi:10.1016/j.yrtph.2010.09.003. Link: <http://bit.ly/ecetoc-art2010-4>

ECETOC reports available for free download: <http://www.ecetoc.org/publications>

¹ TR 106 : Guidance on Identifying Endocrine Disrupting Effects (June 2009) <http://bit.ly/ecetoc-tr106>

² WR 16 and Addendum: Guidance on Interpreting Endocrine Disrupting Effects + Addendum (October 2009) <http://bit.ly/ecetoc-wr16>



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NEW WORKSHOP PLANNED ON RISK ASSESSMENT OF ENDOCRINE DISRUPTING CHEMICALS - CASE STUDIES

Science area:
Reproductive health

+
Risk, hazard and precaution

In their September meeting, the ECETOC Scientific Committee approved a Workshop to further develop the guidance to risk assess endocrine disrupting chemicals, the potency concept, specificity and human relevance. The scheme developed by the Task Force in identifying endocrine disrupting effects has been well accepted and the German

Federal Institute for Risk Assessment (BfR) has also developed a similar scheme. Dr. van Ravenzwaay, Dr. Bars and Dr. Galay-Burgos will organise a smaller group within the same Task Force (tox and ecetox) to develop the criteria further and then share/test it with attendees of the related previous Workshop for discussion.

2 NEW ENVIRONMENTAL TASK FORCES ESTABLISHED

At the October meeting of the Scientific Committee, nominations were reviewed and stewards appointed for two new Task Forces in the environmental science areas. The first meetings have now been fixed.

The Task Force on 'Development of Interim Guidance for the Inclusion of NER (non-extractable residues) in the Risk Assessment of Chemicals' meets for the first time 26th January 2011.

The Task Force on 'Understanding the Relationship between Extraction Technique and Bioavailability' will hold its first meeting 1st February 2011.

Details of these and other Task Forces are available on our website:

<http://www.ecetoc.org/task-forces>

REVIEW MEETING PLANNED ON REACH-DRIVEN SCIENCE NEEDS

Since last January, a small network activity was run by some members of the Scientific Committee to identify areas where scientific opinions need to be further developed for effective implementation of REACH. Now that the registration phase of REACH is finalised, it seems an appropriate time to share the ideas for wider input. Experts within ECETOC member companies that have comprehensive and practical experience with application dossiers will soon be invited for a one-day review meeting (target date: 1 March 2011, venue: Brussels). The aim of this meeting is to develop a mapping of the science issues and decide where to put ECETOC efforts in terms of future Task Forces and Workshops.

AGENDA

December

- 01 189th Scientific Committee meeting, ECETOC, Brussels
- 02 Targeted risk assessment core team meeting ECETOC, Brussels
- 13 Board of Administration meeting Sheraton Brussels Airport Hotel
- 21 Development of guidance for assessing the impact of mixtures of chemicals in the aquatic environment TF teleconference
- 22 Low-dose interactions TF meeting, ECETOC, Brussels

2011

January

- 06 Development of guidance for assessing the impact of mixtures of chemicals in the aquatic environment TF teleconference
- 10 Risk assessment approaches for PBT/vPvB or POPs teleconference
- 24 Cyanides Antidotes TF meeting, ECETOC, Brussels
- 25 190th Scientific Committee meeting, ECETOC, Brussels
- 26 Development of interim guidance for the inclusion of non-extractable residues (NER) in the risk assessment of chemicals 1st TF meeting, ECETOC, Brussels
- 27 Linear polydimethylsiloxanes TF meeting, ECETOC, Brussels

February

- 01 Understanding the relationship between extraction technique and bioavailability 1st TF meeting ECETOC, Brussels
- 04 Risk assessment approaches for PBT/vPvB or POPs TF meeting, ECETOC, Brussels
- 17-18 ERA of ionisable compounds TF meeting, ECETOC, Brussels

March

- 01 Review meeting on REACH-driven science needs, ECETOC, Brussels
- 31 191st Scientific Committee meeting, ECETOC, Brussels



ECETOC YOUNG SCIENTIST POSTER PRESENTATION AWARD AT IUOTOX

This year's Young Scientist Award on human health related research has been awarded to Céline Brochot, INERIS, France, and to Taku Tanaka, University Piacenza, Italy, for their work on combining multimedia models with physiologically based pharmacokinetic (PBPK) modelling as part of the European project 2-FUN. Their work was presented in a poster at this year's meeting of the IUOTOX (International Union of Toxicology) / EUROTOX congress on 19-23 July 2010 in Barcelona. www.iutox2010.org, <http://www.2-fun.org>.

LATEST Publications

Reports:

Technical Report No. 110 Guidance on Assessment Factors to Derive a DNEL (published October 2010) <http://bit.ly/ecetoc-tr110>

Scientific Article:

Bars, R., et al. Science based guidance for the assessment of endocrine disrupting properties of chemicals. *Regul.Toxicol.Pharmacol.*(2010), doi:10.1016/j.yrtph.2010.09.003
Link: <http://bit.ly/ecetoc-art2010-4>



ECETOC In Brief

ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals, was established in 1978 as a scientific, non-profit, non-commercial association. It is financed by 49 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 view our activities and to download our publications

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