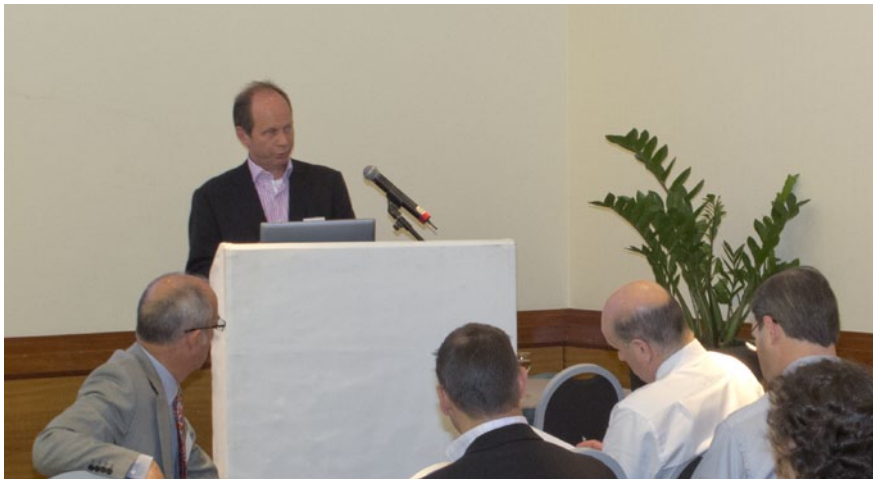
ecetoc e-NEWSLETTER
EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

Issue 23 September 2012

Annual Technical Meeting debates 'Exposure' in Risk Assessment



Gerard Swaen (Dow) - one of four speakers covering 'the present'

For this year's Annual Technical Meeting, ECETOC chose to bring forward the topic of 'Exposure'. Looking at the hazard-side of risk assessment, test methods are already well-developed, and continue to be improved, and a large pool of chemical-specific data available. But exposure is often somewhat orphaned. The programme of the ATM, 'Chemical Exposure for Risk Assessment: Present Problems and Future Solutions', brought together enlightening speakers and stimulated an insightful debate. The lunchtime poster session provided time for networking amongst participants.

The meeting started with the keynote speech by José Tarazona of ECHA on the importance of exposure assessment, in particular under REACH and the CLP regulation. He reviewed how exposure is applied in the chemical registration and evaluation steps, and described how exposure scenarios are being defined through the use descriptors, operational conditions and risk management measures. He also pointed out where he sees the current specific needs to improve exposure assessments, namely on refined methods and tools to address aggregate exposure to multi-constituent and UVCB substances, as well as to address combined exposure to different substances. Thereby, it was important to understand realistic exposure and co-exposure levels.

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Dr Alan Poole to succeed Dr Neil Carmichael as Secretary General

On 1st October 2012, Dr Alan Poole, previously of Dow Europe will succeed Dr Neil Carmichael as Secretary General of ECETOC.

Neil Carmichael will retire from ECETOC at the end of September after 30 years in the chemical industry. In 1982 he joined Dow Chemical in the Netherlands as a toxicologist and moved with them, first to Switzerland and then to the UK. In 1989 he moved to France as Head of Toxicology for Rhone-Poulenc Agro and Director of the Research centre of Sophia-Antipolis, posts he held, successively, with Aventis CropScience and Bayer CropScience.

His association with ECETOC goes back to 1983 with Monograph 6 (published in 1985). He was a member of the Scientific Committee from 1990-2003 and has been Secretary General since November 2006. During this time, Neil brought ECETOC to a new level. With his experience and dedication, he has established ECETOC as a leading organisation in developing scientific answers and new approaches for important challenges in the areas of Toxicology and Ecotoxicology. This has increased the importance of ECETOC in supporting scientific and regulatory development in Europe and also its understanding within the industry. Neil has built a good foundation for ECETOC to even better serve its member companies and address future challenges. This will give the new Secretary General an excellent starting position to further develop the organisation.

Alan Poole earned his B.Sc. in Biochemistry from the University of Cardiff, and his PhD from the University of Surrey: he is also a Fellow of the Royal College of Pathologists. He worked for the UK Medical Research Council studying the modes of action of pulmonary lung carcinogenesis in particular mesothelioma before moving to Smith Kline and French to lead a scientific team involved in preclinical development of ethical pharmaceuticals.

He was later employed by Dow Chemical in Switzerland where he worked for over 20 years addressing safety of industrial chemicals, during which time he participated in many industry and governmental activities. He has published a book on toxicology as well contributing chapters to several others, and has published widely in the scientific literature. Alan is a familiar figure at ECETOC where he has been involved with many of its activities over the years.

SG CORNER

This is my final contribution to the ECETOC newsletter, simultaneous with my retirement, and with that in mind I would like to end on a positive note and with personal opinions.

In the 19th and early 20th centuries, most industrial activities were associated with specific diseases. Donald Hunter's famous "Diseases of Occupations", published in 1955, catalogued many of these, ranging from silicosis in mines to lead poisoning. While I was researching for my PhD on mercury poisoning, I recall the description of mirror makers in Furth and Nuremburg having lost all their teeth as a result of exposure to mercury fumes.

Observational epidemiology used by some particularly astute doctors described specific toxicological syndromes and correctly identified their causes as early as the 18th century. Percival Potts is the most famous with his identification of the carcinogenicity of coal smoke residues experienced by chimney sweeps in London.

In contrast, experimental toxicology is a rather new science and ecotoxicology even newer. The methods for performing these studies were developed mostly during the 1960's and 70's. In fact one of the criticisms often levelled at regulatory toxicology is that it has not developed much since then. Of course this is nonsense; the methods have been constantly developed since that time. While it is true that the process of development of universally agreed regulatory methods is slow compared to that of the science behind it, this has the advantage of not leading to too many "red herrings" in the process.

When ECETOC was first established in 1978 there were no internationally recognised testing guidelines and no published GLP. The first monographs addressed how to identify carcinogens and reproductive toxicants. The first monograph I was involved with discussed alternatives to animals for deriving acute toxicity data (published in 1985).

It seems to me that we are sometimes too self-critical about our methods and their effectiveness. This is largely a result of seeing these studies as "tests" with a "yes or no" outcome. Biology is rarely that simple and the results of these studies require understanding and interpretation. Furthermore, the concepts of potency and exposure have to be applied to that interpretation in order to predict the risk.

This has been the area of greatest progress since ECETOC's foundation and continues to be the core of the task forces' activities. Thus, mode of action has become a key element of toxicological assessment. In the same way, chemical and biological processes have become key to environmental assessment. A casual look at ECETOC's output in the last 5 years will show that these are the areas where we have put the majority of our efforts.

There are challengers to these concepts who would have us believe that our methods are redundant. ECETOC will need to stick to its guns to confront those who claim that dose and potency are irrelevant. There are also challenges to the concept of guideline studies and GLP. We should be careful not to allow our own self-criticism to be seen as supportive of these views. I believe that ECETOC is doing a great job in defending the science of risk assessment. Also, by speaking for the scientists of a large spectrum of industrial sectors, ECETOC is able to present a unified view which demands to be taken seriously. I am confident that ECETOC will continue to occupy this unique position and be recognised by its members for the value of its contribution.

Neil Carmichael

Dr Neil Carmichael
Secretary General

Change of Address
NEW OFFICES FOR ECETOC SECRETARIAT

The ECETOC Secretariat is on the move in mid-September. New offices are currently being fitted out on the same site, but in building 2 instead of the current building 4.

Task Force and Scientific Committee members will benefit from a large conference room, dedicated visitor office and better catering facilities. The move will take place 17th and 18th September during which period there will be disruption to ECETOC's e-mail and telephone system.

Please note our new address as of 17th September 2012 (phone and fax numbers remain unchanged):

ECETOC AISBL
2 avenue E. Van Nieuwenhuyse, Box 8
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Update from ECETOC
TARGETED RISK ASSESSMENT

Following the April launch of version 3 of the ECETOC Targeted Risk Assessment tool and the associated workshop in May, ECETOC published a report in July detailing the changes in the new version: Technical Report No. 114, ECETOC TRA version 3: Background and Rationale for the Improvements. The report can be downloaded free of charge: http://bit.ly/ecetoc-tr114

To resolve issues highlighted in user feedback since the TRAv3 launch, a revised version of the TRAv3 standalone consumer tool was made available early in July. Users of the standalone consumer tool are recommended to replace their earlier copies by this updated version.

A TRA 'Frequently Asked Questions' list is maintained and regularly updated, so users having any issues with the tool should first refer to this before contacting ECETOC. These items, along with the TRA integrated tool, and supporting documentation can all be downloaded free of charge from the website: http://www.ecetoc.org/tra

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Four speakers covered 'the present':

Gerard Swaen (Dow) gave his thoughts about 'exposure as a limiting factor in epidemiology research' mainly due to poor quality data on exposure.

Andrew Sweetman (Lancaster University) addressed 'environmental persistence and exposure assessments' showing that regulatory approaches can present an unrealistic scenario by only looking at single media degradation half-lives.

Kim Travis (Syngenta) spoke about the work of the recently completed task force on 'combined exposures at low doses' whereby exposure concentrations played a critical role, which is often not the case in mixture toxicology.

Marike Kolossa (German UBA) presented current bio-monitoring projects in Germany that are designed to establish 'real' environmental exposure levels to priority pollutants.

'The future' was addressed by another four speakers:

Jonathan Goodman (Cambridge University) in his talk on 'chemical informatics for risk assessment' showed how molecular information can provide valuable information for toxicology and for an understanding of exposure.

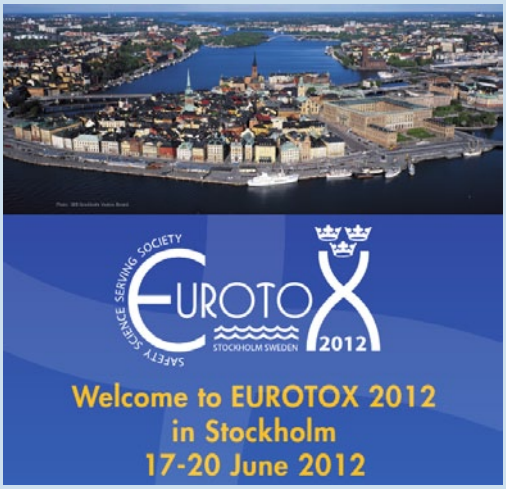
Tim Pastoor (Syngenta) provided an overview of the Risk 21 project that, amongst other topics, postulates the paradigm shift in risk assessment whereby problem formulation begins with exposure estimates rather than toxicity hazard data.

Tim Pastoor and Fraser Lewis, both of Syngenta

Sylvia Jacobi (Albemarle) reviewed the work of another recently completed task force on risk assessment of PBT which described refined methods for their exposure assessments and also identified further research needs.

Jacqueline van Engelen (RIVM) talked about methods and databases to 'understand the nature of consumer exposures to mixtures' and where information needs still lay.

Finally, participants from industry (member and non-member companies), academia and governmental research institutes discussed in two breakout groups where they see research needs to advance exposure science towards improving human and environmental risk assessment. Constructive broad ideas for new activities that ECETOC (or LRI) could undertake emerged. These will be further discussed within the ECETOC Scientific Committee to distil specific project proposals.



ECETOC Session at EUROTOX 2012

For the programme of this year's EUROTOX congress, ECETOC organised a session on 'Dose-response relationship and receptor-mediated toxicology'. Under Remi Bars' (Bayer CropScience) and Ben van Ravenzwaay's (BASF) chairing, five speakers shared the outcome of studies with nuclear receptors, such as CAR/PXR, PPAR, ER, AR, mediating various forms of toxicity.

Earl Gray (US EPA): Endocrine toxicity mediated through ER, AR steriodogenic and AhR pathways. Case studies and dose-response relationship

Russell Thomas (Hamner Institutes for Health Sciences): Genomic dose-response modeling to inform key events in a mode-of-action risk assessment

Remi Bars (BayerCropscience): Endocrine toxicity-mediated through the AR and evaluation of dose-response relationship

Cliff Elcombe (CXR Biosciences): Dose-response relationship toxicity in CAR/PXR humanised mouse

Dieter Schrenk (University Kaiserslautern): Dose-response relationship in toxicity following Ah receptor activation in animal models

This topic addresses an on-going debate which is controversial when exploring the nature of the dose-response curve and the effect at the low end of this curve. The concept of threshold in receptor-mediated toxicity is currently being challenged, particularly in the field of endocrine toxicity. The latest research in the field presented made a valuable contribution to this debate witnessed by the sizeable audience in this session and that engaged in a lively debate.

For more information,
please visit http://www.eurotox2012.org

ECETOC article published in the open literature

RISK ASSESSMENT OF ENDOCRINE ACTIVE CHEMICALS: IDENTIFYING CHEMICALS OF REGULATORY CONCERN

European regulation on plant protection products, biocides and chemicals (REACH) only supports the marketing and use of chemical products on the basis that they do not induce endocrine disruption in humans or wildlife species. There was, however, no agreed guidance on how to identify and evaluate endocrine activity and disruption. In 2009, ECETOC established a task force to develop scientific criteria that could be used within the context of these three legislative documents. The resulting ECETOC technical report (ECETOC, 2009a) and the associated workshop (ECETOC, 2009b) presented a science-based approach on how to identify endocrine activity and disrupting properties of chemicals for both human health and the environment. The specific scientific criteria proposed for the determination of endocrine activity and disrupting properties that integrate information from both regulatory (eco)toxicity studies and mechanistic/screening studies were published in 2011 (Bars *et al*). These criteria combine the nature of the adverse effects detected in studies which give concern for endocrine toxicity with an understanding of the mode of action of toxicity so that adverse effects can be explained scientifically. A key element in the data evaluation is the consideration of all available information in a weight-of-evidence approach. It was recognised, however, that the concept needed to be refined if discrimination between chemicals with endocrine properties of low concern and those of higher concern (for regulatory purposes) was to be achieved.

Following a second workshop (ECETOC, 2011), the guidance was developed further to include a number of additional factors. For human health assessments these include the relevance to humans of the endocrine mechanism of toxicity, the specificity of the endocrine effects with respect to other potential toxic effects, the potency of the chemical to induce endocrine toxicity and consideration of exposure levels. For ecotoxicological assessments, the key considerations include specificity and potency, and also extend to the consideration of population relevance and negligible exposure. This new guidance has now been published in Regulatory, Toxicology and Pharmacology journal (Bars *et al*, 2012). The article is available with Open Access from http://www.sciencedirect.com/science/article/pii/S0273230012001237

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ECETOC. 2009a. Guidance on identifying endocrine disrupting effects. Technical Report No. 106
European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium

ECETOC. 2009b. Guidance on interpreting endocrine disrupting effects. Workshop Report No. 16
European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium

ECETOC. 2011. Risk Assessment of Endocrine Disrupting Chemicals. Workshop Report No. 21
European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium

Bars R, Broeckaert F, Fegert I, Gross M, Hallmark N, Kedwards T, Lewis D, O'Hagan S, Panter G H, Weltje L, Weyers A, Wheeler J R, Galay Burgos M. 2011
Science based guidance for the assessment of endocrine disrupting properties of chemicals. Regul Toxicol Pharmacol 59(1):37-46

Bars R, Broeckaert F, Fegert I, Gross M, Hallmark N, Kedwards T, Lewis D, O'Hagan S, Panter G H, Weltje L, Weyers A, Wheeler J, Galay Burgos M. 2011
Corrigendum to "Science based guidance for the assessment of endocrine disrupting properties of chemicals". Regul Toxicol Pharmacol 60(3):411-412

Bars R, Fegert I, Gross M, Lewis D, Weltje L, Weyers A, Wheeler JR, Galay-Burgos M. 2012
Risk assessment of endocrine active chemicals: Identifying chemicals of regulatory concern. Regul Toxicol Pharmacol 64(1):143-154 (Open Access Article)

Low-dose Interactions Task Force publishes

ECETOC TECHNICAL REPORT 115

Chemical risk assessment is predominantly carried out on individual substances, and this is also reflected in most chemical-related legislation. In reality though, humans, fauna and flora are exposed to a variety of substances concurrently. The toxicology of chemical mixtures is usually addressed through concepts of concentration or dose addition and independent action; synergism is considered to occur only rarely.

More recently, the question arose whether such risk assessment procedures are adequate for assessing combined exposure to multiple chemicals. Much attention is being given to the so-called 'cocktail effect' which is hypothesised to occur due to simultaneous exposure to low levels of environmental chemicals. According to this theory, unexpected effects can occur due to interaction in the body between these chemicals even though the levels could be below the threshold of toxicity for the individual chemicals or their breakdown products. It is claimed that these interactions at low-dose levels may be greater than additive.

An ECETOC Task Force undertook an extensive literature search looking for evidence of such effects at environmental concentrations and multiples thereof, in mixtures tested at or near the NO(A)EL of their single components, and in mixtures tested well below the NO(A)EL of their single components. The findings have now been published in a Technical Report under the specific title: Effects of Chemical Co-exposures at Doses Relevant for Human Safety Assessments.

The report can be downloaded from the ECETOC website free of charge.
Direct link to summary and PDF download: http://bit.ly/ecetoc-tr115

Keep up to date with the latest ECETOC news by following our Twitter feed http://www.twitter.com/ecetoc, or by subscribing to our RSS news feeds at http://bit.ly/ecetoc-rss-news and http://members.ecetoc.org/en/news.aspx

Further steps on the Replacement, Reduction and Refinement (3Rs) of Animal Experiments in Ecotoxicology

Current chemical risk assessment and effluent and water quality monitoring require ecotoxicity testing using vertebrates, in particular fish, amphibians and birds. Due to increased ethical concerns, the development and acceptance of alternative methods is timely. To this end, last 28th-29th June 2012 the "1st European Conference on the Replacement, Reduction and Refinement of Animal Experiments in Ecotoxicology" was successfully carried out in Dübendorf (Switzerland). The conference was organised by Eawag (Swiss Federal Research Institute of Aquatic Science and Technology), one of the partners of EUROECOTOX, a coordinating action funded by the European Community's Seventh Framework Programme.

The conference provided a good platform for young scientists and experts from academia, industry and regulation in the field of 3Rs of animal tests used in environmental risk assessment. It focused on the current state and future directions of the development, implementation and application of the 3Rs, from bench to acceptance. An exciting programme was put in place based on invited key note speakers and presentations from submitted abstracts. A special key note lecture was given by Susanna Louhimies (DG Environment, European Commission) about the establishment of the 3Rs in European Legislation. About 62% of participants were from academia, 22% from industry and 16% from regulators and stakeholders.

The conference had different outcomes when aiming to identify where we stand and what barriers need to be overcome in order to turn the 3Rs in ecotoxicology into practice, especially concerning 5 points:

(I) Experimental Approaches,
(II) Towards Integration and Implementation,
(III) Establishing the 3Rs in European Legislation,
(IV) Perspectives and Initiatives towards the 3Rs, and
(V) Computational Approaches.

A final plenary session discussed the future of alternative methods in ecotoxicology.

The sections (I), (II) and (IV) were stimulated by a key note presentation of an invited expert. A short summary of the conference, programme and abstracts is available from the project website.

The event was co-funded by the European Society of Toxicology in Vitro (ESTIV), who sponsored the participation of ESTIV members and gave two prizes for young scientist's presentation and poster.

A report on the conference has been published and is available from the EUROECOTOX website.

A publication in the open literature is now being prepared with the title 'A European perspective of alternatives to animal experiments for environmental risk assessment'.

ECETOC is a partner in EUROECOTOX. For more information on EUROECOTOX, the network, major goals and activities and on how to join the network, please visit the website via the link at http://www.ecetoc.org or direct at www.euroecotox.eu

2012 YOUNG SCIENTIST AWARDS

In 2012 ECETOC sponsored the following awards for young scientists and is proud to announce this year's winners:

Exposure science related award

The ECETOC 'young scientist' award at X2012 (7th International Conference on the Science of Exposure Assessment, organised by the British Occupational Hygene Society) was awarded to Katleen de Brouwere from Vito in Belgium for her paper 'mechanistic risk assessment of indoor air pollutants: exposure to phthalates'. Katleen successfully applied the methodology developed in the context of TAGS by Dr Alberto Gotti and Dr Spyros Karakitsios of CERTH (GR). The X2012 jury all agreed that Katleen's paper was of a very high standard and that the concepts she addressed (which arise from the CEFIC-LRI supported TAGS project) take the science of multi source, multi pathway consumer exposure and risk assessment to a new level. Indeed there was much subsequent discussion on how the concepts might also be applied to worker and environmental exposures. For more information on the 7th International Conference on the Science of Exposure Assessment, visit www.x2012.org

Environmental science related award

The ECETOC Best Platform Award honours the early career scientist with the best platform presentation at the SETAC Europe Annual Meeting. The award winner receives a free registration to the next SETAC Europe Annual meeting and travel and accommodation support. She/he also receives a free SETAC membership.

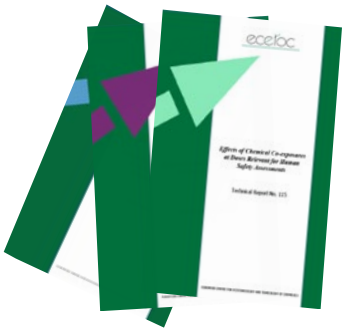
This year's Best Platform Award has been awarded to Dorothea Gilbert, Aarhus University, Denmark, for her talk entitled: Passive dosing under the microscope reveals that microorganisms enhance the mass transfer of hydrophobic organic chemicals. http://berlin.setac.eu/

Human health science related award

This is a Best Poster Award for toxicological research into mechanisms and risk assessment, selected by a panel in which ECETOC participates. The winner receives a monetary prize and a free invitation to the following year's EUROTOX meeting.

This year's Young Scientist Award on human health sciences, presented at the EUROTOX annual meeting in Stockholm, Sweden, has been awarded to Camille Béchaux, Anses France for her poster presentation on: Dynamical modeling of dietary exposure to dioxins and corresponding present and future health risk: A case study in France. http://www.eurotox2012.org

Latest PUBLICATIONS



All ECETOC reports are freely available from our website: www.ecetoc.org/publications

Technical Reports

TR 114: ECETOC TRA version 3: Background and Rationale for the Improvements (Published July 2012)

TR 115: Effects of Chemical Co-exposures at Doses Relevant for Human Safety Assessments (Published July 2012)

Workshop Reports

WR 23: Epigenetics and Chemical Safety
5-6 December 2011, Rome (Published May 2012)

Scientific Articles

Bars R, Fegert I, Gross M, Lewis D, Weltje L, Weyers A, Wheeler JR, Galay-Burgos M. 2012.
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Regulatory Toxicology and Pharmacology 64(1):143-154
Doi: 10.1016/j.yrtph.2012.06.013 (Open Access Article)

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Use of 'Omics to Elucidate Mechanism of Action and Integration of 'Omics in a Systems Biology Concept.
Mutation Research - Genetic Toxicology and Environmental Mutagenesis 476(2)
Doi: 10.1016/j.mrgentox.2012.04.004

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An overview of values for the threshold of toxicological concern.
Toxicology Letters 211(3):296–303
Doi: 10.1016/j.toxlet.2012.03.795

Agenda

Dates and times are subject to change.
Please check our website for the latest information.

September

11-12	Brussels, Belgium 199th Scientific Committee Meeting
17	Warsaw, Poland. ECETOC Symposium 'Epigenetics and Chemical Safety' at 42nd EEMS Annual Conference
17-18	ECETOC moves to new offices New address: Avenue E. van Nieuwenhuyse 2, 1160 Brussels Belgium
25-26	Sophia Antipolis, France. TF: Mode of Action and Identification of Adverse vs. Non-adverse Effects third meeting

October

18	Venue TBC. The application of CBB in RA: Final TF meeting
19	Sharnbrook, UK. Development of interim guidance for the inclusion of non-extractable residues (NER) in the risk assessment of chemicals. TF meeting

November

05	Brussels, Belgium ECETOC Board meeting
06-07	Paris, France. ECETOC Workshop: Assessing Environmental Persistence Brussels, Belgium
08	200th Scientific Committee Meeting

December

18	Brussels, Belgium 201st Scientific Committee Meeting

ECETOC at a glance

Established in 1978, ECETOC is Europe's leading industry association for developing and promoting top quality science in human and environmental risk assessment of chemicals. Members include the main companies with interests in the manufacture and use of chemicals, biomaterials and pharmaceuticals, and organisations active in these fields.ECETOC is the scientific forum where member company experts meet and co-operate with government and academic scientists, to evaluate and assess the available data, identify gaps in knowledge and recommend research, and publish critical reviews on the ecotoxicology and toxicology of chemicals, biomaterials and pharmaceuticals.

ECETOC also provides scientific representation for its member companies through presentations at specialist meetings and by participation in the scientific activities of international agencies, government authorities and professional societies. A non-profit, non-commercial and non-governmental organisation, ECETOC prides itself on the objectivity and integrity of its work programme, the output of which is published in the form of peer-reviewed reports and articles in peer-reviewed journals, or as specialised workshops.

EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

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