ecetoc e-NEWSLETTER
EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS
Issue 21 November 2011

Workshop reviews
COMBINED EXPOSURE TO CHEMICALS

A well-attended workshop on the topical subject 'mixtures' took place this July in Berlin. Over the course of two days, sixty-six invited experts from academia, regulatory bodies and industry reviewed key scientific areas relevant to the assessment of combined exposures to chemicals, discussed reliable and pragmatic approaches to their risk assessment and areas where the science may need further development.

Workshop group photo

IN THIS Issue

The Workshop Participants agreed on the following overall conclusions.

In the last 10 years, there has been a significant amount of research into the toxicology of mixtures and co-exposure, which has genuinely increased our understanding. Participants at the workshop generally agreed that the WHO/IPCS framework provides a useful tool for risk assessment of combined exposure to multiple chemicals from multiple sources. A suitable problem formulation at the outset of any risk assessment of combined exposures to multiple chemicals was thought to be a fundamental first step.

There was overall recognition that, according to available evidence, in practice the toxicity of mixtures in the environment is often dominated by a few of their components, and that these can be identified by available approaches. In this regard, where relevant data are available, the Maximum Cumulative Ratio approach is a useful tool for both human health and environmental risk assessments.

The current state of knowledge shows that

Continued on page 2

SG CORNER:
Science in Society

When ECETOC revised its Science Strategy last year, it retained the area 'Science in Society', however, it was not one of the areas which received the strongest support. The most probable reason for this is that the concept is less self-evident than some of the other science areas.

However, in my view, 'Science in Society' is critical to the effectiveness of ECETOC. Simply put, it is about the societal relevance of what we do and our ability to put our arguments across. Factors which influence our ability to do this include the credibility of industry science and our ability to communicate in ways which make our science meaningful.

The main activities in this area, so far, have been in the areas of 'Socio-economic analysis' and in 'bias and credibility'. The first of these deals with cost and benefit in environmental risk. The second requires addressing sources of bias and identifying the means to detect and neutralise such bias.

ECETOC's main activities in this area go back to June 2008 when we held a workshop at the Annual Technical Meeting entitled: 'Counting the Costs and Benefits of Chemical Controls: Role of Environmental Risk Assessment in Socio-Economic Analysis'. This workshop led to a taskforce which has recently reported (TR113).

Also in 2008 (October) at the EUROTOX meeting in Rhodes, we hosted a session entitled: 'The role of science in society and industry sponsorship of environmental and health research' with eminent speakers from Academia and industry. This session elicited such interest that EUROTOX invited us to consider a follow up session.

Accordingly, ECETOC organised a workshop this August at EUROTOX 2011 in Paris entitled: 'Science in Society: improving the credibility of research in health and environmental science'.

Despite being one of four parallel sessions, there was 'standing room only' in our meeting room. The four speakers selected different aspects of this subject leading to a very lively discussion.

Continued on page 2

Workshop on combined exposure to chemicals, continued from front page...

synergy (exceeding additive effects) is rare and appears to be toxicologically significant only at doses at which there is significant toxicity of one or more of the individual components in the combination. The available data indicate that synergy does not normally occur at environmental concentrations of man-made chemicals. For chemicals that have different modes of action, there is currently very little data to support the occurrence of combination effects below their individual predicted no-effect levels. However, in the absence of information on mode of action, dose / concentration addition can be used as the conservative default.

The discussion at the workshop identified a number of areas that require further research, such as better understanding of mode of action, improved methodologies of exposure assessment including assimilation of better databases and data processing methods. The threshold of toxicological concern approach and non-testing methods were suggested as potentially useful tools that also need further development for use in this context.

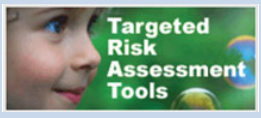
In recent years, there has been growing public perception and concern about the possibility of 'cocktail effects' of chemicals at very low doses of the single substances (i.e. below levels deemed to be safe for humans and the environment) which are generally not taken into account in regulatory risk assessment. The current evidence offers little support for this; although some of the workshop participants were of the opinion that the current knowledge on combined exposure and effects was too limited to allow such a conclusion. It is important that combined exposures be considered in risk assessment practice – through the use of science-based, targeted and pragmatic tiered approaches. Such approaches should allow identification of any combinations which may require priority attention.

Whilst recognising the importance of addressing the potential risk of combined exposures to chemicals, this should perhaps be seen in light of the various other scientific areas that are important for protecting and improving human health and the environment. However, some workshop participants felt that this view is a general one, which does not only concern the issue of combined exposure and effects of chemicals. Overall though, the use of a tiered approach is strongly recommended to ensure optimum use of resources. The findings of the workshop have been published as ECETOC Workshop Report No. 22, available from the ECETOC website: direct link http://bit.ly/ecetoc-wr22.

Dr Christa Hennes
Health Sciences Manager

Dr Malyka Galay Burgos
Environmental Sciences Manager

Science area:
Mixtures and co-exposure



TARGETED RISK ASSESSMENT TOOL UPDATE

Since its launch in 2004, the ECETOC Targeted Risk Assessment Tool has proved to be an overwhelming success. Since the release of the TRA version 2 in July 2009, over 10,000 downloads of the tools have been made and many of the major consortia placed the TRA at the heart of their 2010 REACH Registrations. Following the first wave of registrations, the core group of the ECETOC Targeted Risk Assessment task force has been seeking feedback from users of the tool in order to identify areas where the tools' functionality and accuracy might be further improved.

At the same time, ECHA has signalled its intent to update its Chesar CSA/ES tool. In this respect, the updates to the worker and consumer tools are being developed in close co-operation with ECHA, who intend to incorporate the two human health components of the TRA into the new Chesar version 2. In addition to these two components, a spreadsheet implementation of EUSES is included in the integrated part of the TRA to facilitate environmental assessments. The integrated part of the TRA is also being updated. These new versions are currently being tested against the TRAv2 and other exposure models.

The intention is to launch the new TRA version 3 in December 2011 together with updated user guides to reflect the changes. A series of workshops for stakeholders, to be organised both by ECHA and ECETOC, are also being planned to inform the constituency of the changes, as well as a supplement to Technical Report 107.

www.ecetoc.org/tra

Dr Malyka Galay Burgos
Environmental Sciences Manager

SG Corner, Continued from front page...

Dr Gerard Swaen from Dow and ECETOC Scientific Committee presented the ECETOC initiative to have observational epidemiology studies registered to reduce publication and reporting bias and increase transparency regarding study design.

Professor Peter Calow of the University of Nebraska and latterly of the ECETOC Scientific Committee emphasised that all scientists are subject to bias and this should be systematically taken into account. The most important tools for this were transparency of study design and rigorous peer review.

Dr José Tarazona from the European Chemicals Agency, Risk Assessment Committee, described mechanisms put in place in the new regulatory frameworks of REACH and CLP. He described the ways of working in these committees to avoid conflict of interest and emphasised the assurance of transparency which came from publication of committee decisions.

Finally Professor Helen Håkansson from the Karolinska Institute in Sweden presented a concept of unified standards for the training of risk assessors with a view to raising scientific standards in this area.

Judging by the interest shown by the attendees, this area is considered to be important by many professionals in the field of risk assessment. Hopefully with initiatives like these, the discussion can move from finger pointing to a more constructive debate on mechanisms to reduce the impact of bias on decisions.

For ECETOC, Science in Society will remain a key area, even if sometimes difficult to grasp. The emphasis will need to be on clarity, consistency and objectivity. We should not just require it of ourselves, but of our fellow scientists also.

Dr Neil Carmichael
Secretary General

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www.ecetoc.org
for more information about ECETOC and to freely download its publications.

Please e-mail us at
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with any enquiries

EEMS 2011 SYMPOSIUM: RISK ASSESSMENT OF ENDOCRINE DISRUPTING CHEMICALS

Barcelona, 6 July 2011

Science area: Reproductive health

Jointly organised by ECETOC and the European Environmental Mutagen Society (EEMS), the symposium was held on the third day of the annual meeting of EEMS in Barcelona with ECETOC being the sole sponsor. The syposium was well received by the more than 80 (out of 240) participants, leaving room for questions after each of the 6 presentations and a lively general discussion at the end.

Ir Vrijhof, co-chair with Dr David Kirkland (EEMS), opened the symposium with a brief introduction of ECETOC and its common history of symposia with EEMS for more than 10 years. The special issues from these symposia form critical state-of-the-science reviews that have been published in the open literature.

Dr Kirkland explained that the connection between genotoxicity / mutagenicity and endocrine disruption (ED) caused by chemicals may not be obvious at first glance. There are, however, two firm links: (i) both represent general modes of action related to carcinogenesis and the induction of reproductive effects, and (ii) in current risk assessment approaches (at least in the EU) hazard identification is immediately followed by regulatory action, without taking exposure into account (basically non-threshold risk assessment approaches). As there is currently no scientific evidence for the absence of a threshold for endocrine mediated effects, ECETOC organised two workshops to review the definition and discuss the risk assessment of ED chemicals. Highlights of these workshops (Barcelona, June 2009; Firenze, May 2011) were presented at the EEMS symposium.

Dr. van Ravenzwaay started the symposium with a historical perspective on ED based on the effects noted in the late 1980's with Vinclozoline. This was followed by an introduction into novel technologies to efficiently identify EDs. Prof. Dekant then continued with an overview of the toxicodynamics and the importance of kinetics for EDs and he proposed to apply normal risk assessment procedures to ED chemicals. Dr. Lewis provided an overview of the results of the first ECETOC workshop which addressed the question how to identify an ED using the Weybridge definition of ED. What is basically required is that adverse effects noted in an apical animal study are clearly linked with an endocrine mode of action.

Dr. Dewhurst then proceeded to present the joint CRD-BfR (UK-German health authorities) view on how to perform a risk assessment of EDs within the current EU legislation. The key element in discriminating between EDs of concern and those of high concern (those requiring risk reduction measures) is the potency of the effect. The UK and Germany propose to use the well-known and accepted specific target organ toxicity (STOT) criteria for systemic toxicity to define potency.

Prof. Benahmed presented important and new scientific aspects of the effects of EDs on reproduction. These included specific windows of sensitivity as well as findings from transcriptomics studies. Finally Dr. Fegert presented the ECETOC concept of risk assessment of EDs, lastly reviewed at the workshop Firenze. The ECETOC concept includes the same elements as proposed by CRD & BfR, but, in addition also takes into account the specificity of the effect (i.e. the dose levels at which ED effects are noted relative to general toxicity).

In his closing remarks, Dr. van Ravenzwaay reminded EEMS participants that the general agreement at both workshops was that a proper risk assessment of chemicals causing adverse effects mediated through an endocrine mode of action is the best way to assess their safety. The concepts proposed are attempts to introduce elements of risk assessment into a law which has neglected this key element in toxicology. This was followed by a general debate among the audience. The agreement at the end was that there is no scientific reason why ED should be treated differently from any other mode of action that has a threshold. Thus, there is no reason not to apply a risk assessment approach, i.e. the initial proposal made by Kirkland and Dekant was not challenged.

Ir Henk Vrijhof
Chemicals Programme Manager

SCIENTIFIC COMMITTEE NEWS

Over the summer, scientists in ECETOC member companies have been working hard to provide detailed comments on four draft reports and opinions from organisations whose work is of great significance to the chemical industry.

OECD Report on 'Novel Endocrine Assays and Endpoints'

The request for comments on a 'Detailed Review Paper on the state of the science on novel *in vitro* and *in vivo* screening and testing methods and endpoints for evaluating endocrine disruptors' had a deadline of 1st September. Comments were compiled with input from the (former) task force on 'Endocrine Disrupting Effects' and submitted via BIAC.

DG SANCO SCs Preliminary Opinion on 'Toxicity and Assessment of Chemical Mixtures'

The two ECETOC task forces on the 'Mixtures' topic: 'Low-dose interactions' and 'Development of guidance for assessing the impact of mixtures of chemicals in the aquatic environment' compiled comments on this preliminary opinion. A collated set of comments were submitted prior to the deadline of 9th September.

EFSA Draft Scientific Opinion 'Exploring options for providing preliminary advice about possible human health risks based on the concept of Threshold of Toxicological Concern'

Member company experts on the TTC concept have given input to comments sent to EFSA prior to the deadline of 15th September.

Comments on Draft OECD TG 426

Following circulation of a draft document on 'Risk assessment of developmental neurotoxicity: evaluation of test guidelines and guidance documents' and 28 specific questions for reviewers in June, ECETOC sent extensive comments to Prof. Håkansson (Karolinska Institute).

To those interested, the specific comments made via ECETOC can be provided by the ECETOC secretariat upon request.

Dr Fraser Lewis
Scientific Committee Chairman

ECETOC publishes report on ENVIRONMENTAL IMPACT ASSESSMENT FOR SOCIO-ECONOMIC ANALYSIS OF CHEMICALS

Science area: Science in society

"...This report draws attention to a number of possible scenarios whereby the outputs of risk characterisations might be linked to quantified ecological impacts through such methods as species-sensitivity analysis, smart modelling, making connections to ecological quality status and using an ecosystem services approach..."

Under REACH, there are provisions to use Socio-Economic Analysis (SEA) to grant an authorisation to substances of very high concern (Article 60); and in decisions about restrictions (Article 68). Similar provisions are used as derogations in the EU water and environmental liability legislation. This requires that the benefits from environmental protection should be greater than the costs for the action to be worthwhile. For industry, SEA may be the only route for countering proposals for no authorisation and for moderating proposals for restrictions. Therefore, it depends crucially on having the risks expressed in ways that can be valued, i.e. in terms of units of life or ecology saved by the banning or the restrictions.

The topic was already discussed at an ECETOC Workshop in June 2008 (WS Report 13), and this evolved then into forming a Task Force with a broad representation of risk assessors and (environmental) economists. The Task Force was charged with reviewing relevant existing principles and practices on Environmental Impact Assessment and establishing a user-friendly framework for use in a SEA focusing on REACH. Under the chairmanship of Prof Peter Calow, now University of Nebraska Lincoln, and with ECHA as observer and adviser, the Task Force has now completed its work which has been published as Technical Report No. 113.

The focus of the report is on the ecological impacts of chemicals rather than on their human health impacts. It is the former where many of the most profound challenges are, and the ECHA guidance for socio-economic analysis associated with both restrictions and authorisation in the REACH process identifies the need for more work in this area. The report argues for as much quantification as possible, with the ideal of monetisation so that a cost-benefit analysis can be carried out. However, there are enormous challenges in ascribing monetary values, especially to non-marketed ecological goods or services. This report draws attention to a number of possible scenarios whereby the outputs of risk characterisations might be linked to quantified ecological impacts through such methods as species-sensitivity analysis, smart modelling, making connections to ecological quality status and using an ecosystem services approach. To date, however, none of these methods is developed to the extent that they could be easily applied. Thus, there will be a need for pioneering efforts in these areas.

Dr Christa Hennes
Health Sciences Manager

The report can be freely downloaded from the ECETOC website: direct link http://bit.ly/ecetoc-tr113

TWO NEW TASK FORCES being established

At its September meeting, the Scientific Committee agreed terms of reference for two new task forces:

'Categorisation Approaches, Read-across, (Q)SAR'

'Poorly Soluble Particles/Lung Overload'

Calls for nominations have been sent to ECETOC member companies, and the task forces are expected to start in January. Details can be found on the ECETOC Members' website (for ECETOC members only): http://members.ecetoc.org

OTHER ECETOC REPORTS in press

The following reports will be published mid-November:

- Technical Report No. 111: Development of guidance for assessing the impact of mixtures of chemicals in the aquatic environment. The task force of the same name publishes their findings.
- Technical Report No. 112: Refined Approaches for Risk Assessment of PBT/vPvB Chemicals. The PBT task force explores opportunities to progress the science in this area.
- Workshop Report No. 21: Risk Assessment of Endocrine Disrupting Chemicals. 9-10 May 2011, Florence. 38 experts discussed approaches for the risk assessment of endocrine disrupting chemicals.

See back cover for links to Summaries and PDF downloads.

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Workshop to examine
EPIGENETICS AND CHEMICAL SAFETY

Rome, 5-6 December 2011

"The workshop will address the relevance of epigenetic changes to the evaluation of chemicals, and examine scientific and technological approaches to identifying and quantifying the epigenetic effects of chemicals."

ECETOC will hold a 2-day workshop in Rome (Italy) on the 5th and 6th December 2011, to discuss epigenetics and chemical safety.

With the increased attention to and interest in epigenomics in the scientific community, this field is rapidly evolving but is still at a relatively early stage with respect to its application in (eco)toxicology. Currently, epigenetic testing is insufficiently validated in order to be included into the regulatory process of chemicals. For example, there is no single test available for determining epigenetic effects, and there is an incomplete understanding of the normal DNA-modification patterns and long-term effects such as to the public health. In addition, a screening scheme to prioritise chemicals through epigenetic analysis has not been developed. Epigenetic changes can be triggered by environmental factors, e.g. exposure to metals, persistent organic pollutants or endocrine disrupting chemicals has been shown to modulate epigenetic marks, not only in mammalian cells or rodents, but also in environmentally relevant species such as fish or water fleas.

In order to increase our understanding of the science of epigenetics and its potential role in (eco)toxicology and risk assessment, a solid understanding of the biology and variation in the epigenome is essential to eliminate concerns about possible adverse health effects related to epigenetic changes. In particular, very little is known about which epigenetic alterations are part of normal variability and what could be considered adverse and, hence, pose a health risk. Still under debate is the extent to which the fundamental principles that guide toxicology, such as relevant doses, dose-rates, routes of exposure, and experimental models, should to be taken into consideration in the design and interpretation of epigenomic studies.

The workshop will address the relevance of epigenetic changes to the evaluation of chemicals, and examine scientific and technological approaches to identifying and quantifying the epigenetic effects of chemicals. This will help to assess their potential effects on human health and the environment. A series of breakout groups will address specific questions and their findings will be presented and discussed at a plenary session. The outcome will be published in an ECETOC workshop report.

http://bit.ly/ecetoc-ws-2011-epigenetics

Dr Malyka Galay Burgos
Environmental Sciences Manager

ECETOC LAUNCHES 6 LANGUAGE OPTIONS FOR ITS WEBSITE CONTENT.

ECETOC has been developing a number of 'mini websites' to offer part of its content in a range of languages. The first group comprises French, German, Italian, Spanish, Chinese and Japanese. Other language options and more translated content will be rolled-out in the near future. The language sites will be available via a drop-down menu on the homepage www.ecetoc.org.

YOUNG SCIENTIST AWARDS 2011

This year's Young Scientist Award on human health sciences research, presented at the EUROTOX annual meeting, has been awarded to Amy Zmarowski of NOTOX, Netherlands, for her poster presentation: 'Differential effects of methylazoxymethanol and MK-801 administration on learning and memory impairment in Sprague Dawley and Wistar Han rats'.

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 price and a free invitation to the following year's EUROTOX meeting.

Dr Christa Hennes
Health Sciences Manager

Latest Publications

Technical Reports:

TR No. 111 Development of guidance for assessing the impact of mixtures of chemicals in the aquatic environment. (To be published mid-November 2011). For summary and PDF download once published: http://bit.ly/ecetoc-tr111

TR No. 112 Refined Approaches for Risk Assessment of PBT/vPvB Chemicals (To be published mid-November 2011). For summary and PDF download once published: http://bit.ly/ecetoc-tr112

TR No. 113 Environmental Impact Assessment for Socio-Economic Analysis of Chemicals: Principles and Practices (Published August 2011) For summary and PDF download: http://bit.ly/ecetoc-tr113

Workshop Reports:

WR No. 21 Risk Assessment of Endocrine Disrupting Chemicals 9-10 May 2011, Florence. (To be published mid-November 2011). For summary and PDF download once published: http://bit.ly/ecetoc-wr21

WR No. 22 Workshop on Combined Exposure to Chemicals 11-12 July 2011, Berlin (Published October 2011) For summary and PDF download: http://bit.ly/ecetoc-wr22

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

Agenda

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

November

09-10 ERA of ionisable compounds: task force mtg
Unilever, Colworth, UK

15 194 Scientific Committee mtg
ECETOC, Brussels, Belgium

16-17 Cefic LRI Annual Workshop
Brussels, Belgium

21 The application of CBB in RA: task force mtg. Academy of Medical Sciences, London, UK

22 Task forces joint mtg: NER + Extraction Technique & Bioavailability
Shell Centre, London, UK

24 Low-Dose Interactions: task force mtg
ECETOC, Brussels, Belgium

28 Potency in carcinogenicity and reproductive toxicity classification: task force mtg
ECETOC, Brussels, Belgium

December

02 Board of Administration mtg
ECETOC, Brussels, Belgium

05-06 Workshop: Epigenetics and Chemical Saftey. Rome, Italy

15 195 Scientific Committee mtg
ECETOC, Brussels, Belgium

January 2012

04 RA of Genotoxic carcinogens: task force mtg
Dow Europe, Horgen, Switzerland

ECETOC (**European Centre for Ecotoxicology and Toxicology of Chemicals**) was established in 1978 as a scientific, non-profit making, non-commercial association and counts as its members the leading companies with interests in the manufacture and use of chemicals. An independent organisation, ECETOC provides a scientific forum through which the extensive specialist expertise of manufacturers and users can be harnessed to research, evaluate, assess, and publish reviews on the ecotoxicology and toxicology of chemicals, biomaterials and pharmaceuticals.

Smartphone QR Code:

ECETOC contact details

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