ecetoc

e-NEWSLETTER

EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

No. 16, March 2010

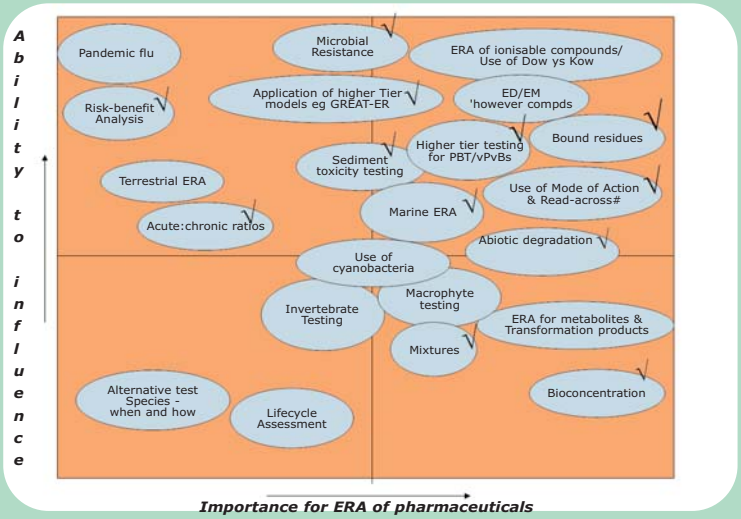
Strategic Science Area: Exposure issues

ECETOC LAUNCHES NEW INITIATIVES RELATED TO PHARMACEUTICALS AND THE ENVIRONMENT

Since its establishment in 1978, ECETOC's membership has included pharmaceutical companies, chemical companies with significant consumer and personal care portfolios and food companies as well as chemicals, petrochemicals and agrochemicals. However, it came to it's attention recently that there were options for sector specific activities such as, for example, in the pharmaceutical sector that were not yet fully explored.

Accordingly, a meeting was organised in Brussels to discuss ways in which ECETOC could address the underlying science issues relevant to human and environmental risk assessment (ERA) of pharmaceuticals.

Science areas relevant to pharmaceutical ERA



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15 different companies (23 attendees in all) were invited to participate. During the discussions, seven priority topics were highlighted, of which 3 were prioritised and specific activities have now been initiated.

They are:

- **Bound Residues:**
  A workshop was organised in Brussels in October and a further task force is due to start in 2010
- **ERA of ionisable compounds:**
  A task force is due to start in 2010
- **Read across/MoA/QSAR:**
  A pharma-specific task force is due to start in 2010

SG CORNER

This year the Annual General Meeting (AGM) and the Annual Technical Meeting (ATM) will be held together as a one day event in Brussels on the 8th of June. We hope to make this combined meeting into a highly enjoyable and interesting event, with maximum member participation, so please put the date in your diaries!

The ATM will be in the form of a workshop to review the ECETOC Science Strategy. The last occasion for such a review was 2006, which we called the 'futures workshop'. At the time it was not anticipated that there would be another review so soon. However, much has happened in the interim: REACH is up and running and the largest economic crisis since the great depression has hit industry worldwide. Meanwhile, several European directives have been revised (pesticides, cosmetics) and many areas of science relevant to ECETOC's activities have moved forward. In particular, computational techniques and the approach known as 'systems biology' are promising new developments whose impact on risk assessment is as yet unmeasured.

Perhaps, some of the areas which seemed to be high priority in 2006 will not be retained for 2011; this may be because we have adequately addressed them or simply that their importance has faded and been replaced by other priorities.

We will be surveying member companies, and others who know us, in preparation for (our science strategy review); If you receive the survey, please take the 5 minutes needed to complete it!

We will be surveying member companies, and others who know us, in preparation for this event. If you receive the survey, please take the 5 minutes needed to complete it. This information will be invaluable for our discussions.

We hope that these events will attract a large participation from members and a more detailed program will be sent within a few weeks. Please try to come!

Neil Carmichael

Dr. Neil Carmichael
Secretary General

SCIENTIFIC COMMITTEE NEWS

The Scientific Committee is a central organ of ECETOC, meeting 6 times a year to peer-review and guide the work programme. ECETOC members have access online todetailed minutes of each meeting. It is the intention of this column to share key committee developments since the last newsletter with our subscribers

Committee adopts 'Guidance on Assessment Factors to Derive DNELs' report

In December, the Science Committee adopted a Technical Report on 'Guidance on Assessment Factors to Derive DNELs' (derived no effect levels), subject to a few revisions and further editing. Prepared by a task force at short notice, the report lays out a practical basis by which industry will be able to refer to a science-based approach for consistent and reliable identification of suitable Assessment Factors (AFs).

A critical comparison of AFs contained in the REACH Technical Guidance Documents (TGD) with those identified in ECETOC Technical Report 86 (Derivation of Assessment Factors for Human Health Risk Assessment) has been undertaken, and the criteria been described for applying alternative ('informed') AFs, i.e. different to those contained the REACH TGD. Concerning the guidance on the derivation of DNELs based on human data, the conclusions from ECETOC Technical Report 104 (Framework for the Integration of Human and Animal Data in Chemical Risk Assessment) were taken into account. In addition, the report contains a number of worked case studies to show how the different approaches, i.e. assessment factors, can lead to different DNELs.

The finalised report will form the basis of a workshop to disseminate the DNEL guidance to a wider audience. The workshop will take place 25 March 2010 in Barza d'Ispra, Italy.

RiskBase project comes to an end

The FP6 project: 'Towards Risk-Based Management of European River Basins (RiskBase)' has come to an end. Dr. Andrew Riddle (AstraZeneca) has represented ECETOC in the project's advisory board and has recently shared the final report on its deliverables.

RiskBase has aimed to review and synthesise the outcome of previous EU Framework Programme projects, and other major initiatives, on integrated risk-assessment based management of the (ground-) water-sediment-soil system at river basin scale. The final report of the project lays out key guiding principles for a risk-based management of river basins.

Dr. John Doe
Scientific Committee Chairman

Strategic Science Area: Risk, hazard & precaution

EXISTING MARINE BIODEGRADATION DATA AND IT'S USE IN ENVIRONMENTAL RISK ASSESSMENT

In 2003, risk assessment in the EU was extended to include the marine environment. This acknowledged that there are additional concerns for the risk assessment of the marine environment which may not be adequately addressed in the methodologies used for freshwater environments.

In recognising this increased focus on protecting the marine environment, a task force was established as part of ECETOC's on-going activities to improve understanding of the persistence of chemicals in the environment. The task force compared the available marine, estuarine and freshwater biodegradation data to determine if a scientific basis for extrapolation between the environmental compartments existed.

Quality control and assurance criteria were established for the identification of suitable non-standard biodegradation test data and the ECETOC Marine Biodegradation Kinetics database (EMBK), which consists of >800 data, was prepared. These data have been used to review the scientific basis of the REACH default values and the task force has concluded that the default rate constants for readily biodegradable chemicals should be reconsidered when the next revision of the REACH technical guidance documents is conducted.

Strategic Science Area: Exposure issues

WORKSHOP DEBATES SIGNIFICANCE OF BOUND RESIDUES IN ENVIRONMENTAL RISK ASSESSMENT

Bound residues, including non-extractable residues, are an important factor in PBT assessment and the risk assessment of chemicals. Precautionary risk assessments usually assume 100% bioavailability i.e. all of the chemical present is available, for degradation or to have potential toxic effects on the biota. This precautionary approach generally overestimates the exposure concentration by the amount that is not available and therefore overestimates the level of risk to biota in the environment. Although it is a position that has been recognised and referenced by REACH (2008) and OECD test guidance (2002), there is no agreed guidance on how to determine what is available and what is not, and how information on bound residues should be interpreted in the risk assessment. As a result, it continues to be debated from a scientific and regulatory point of view.

ECETOC held a 2-day workshop attended by 38 stakeholders representative of industry, academia and regulatory authorities from the USA, Canada, Europe and Asia in Brussels on 21-22 October to further this debate and to develop guidance on how to account for bound residues and bioavailability in environmental risk assessment. The conclusions, future regulatory and research needs and a framework outlining a possible approach for advancing and improving the risk assessment of bound residues will shortly be published in Workshop Report No 17.

Strategic Science Area: Risk, hazard & precaution

WORKSHOP EXAMINES HOW MoA DATA CAN BE USED TO MODIFY HUMAN RISK ASSESSMENT

A workshop entitled 'Using Mode of Action (MoA) Information to Improve Regulatory Decision Making' was held 2-3 November at the city presentation centre in London. This event was organised in cooperation with HESI, and was sponsored by Cefic LRI.

The main goal of the meeting was to examine to what extent toxicological mode of action information can be used to modify human risk assessment. This approach evaluates the known key steps in the toxicological mode of action in animals with the available information on the relevance of this pathway in man. The discussion centred on the 'mode of action framework' which is promoted by WHO International Programme on Chemical Safety and is similar to the approach proposed by ECETOC in Technical Report No. 99 – 'Toxicological Modes of Action: Relevance for Human Risk Assessment' which was published in 2006. Presentations were made by a distinguished group of speakers from academia and industry, which used case studies to illustrate the practical use of the framework.

There was a high level of agreement on using this approach where sufficient information is available to characterise a 'mode of action'. There was, of course, some debate as to how much data would be needed to establish a 'known mode of action', which could then be extrapolated from one example to less thoroughly investigated chemicals. One of the main recommendations coming from this meeting was the establishment of a register of those modes of action which are sufficiently well described as to be useful in employing this approach in risk assessment within a regulatory context.

ECETOC'S GUIDANCE FOR THE CLASSIFICATION OF CARCINOGENS UNDER GHS PUBLISHED IN *CRITICAL REVIEWS IN TOXICOLOGY*

Strategic Science Area: Risk, hazard & precaution

Last year an ECETOC task force finalised guidance on how to classify carcinogens under the criteria for a globally harmonised system of classification and labelling of chemicals (GHS) developed by the United Nations Conference on Environment and Development (UNCED). The paper has just been published in *Critical Reviews in Toxicology* (see latest publications).

With regard to carcinogenicity, GHS distinguishes between Category 1 ('known or presumed human carcinogens') and Category 2 ('suspected human carcinogens'). Category 1 carcinogens are divided into Category 1A ('known to have carcinogenic potential for humans'), based largely on human evidence, and 1B ('presumed to have carcinogenic potential for humans'), based largely on experimental animal data. Concerns have been raised that the criteria for applying these carcinogenicity classifications are not sufficiently well defined and potentially allow different conclusions to be drawn.

Classification under GHS, like other systems in place, is for hazard, there being no consideration of potency or risk assessment, including exposure considerations. Such elements are being taken into account in the ECETOC scheme. A wide range of carcinogenic potency can be observed both in human epidemiological studies and in animal experiments. The following cut-off values for high and low potency for different exposure scenarios are proposed:

Cut-off values for substances of high and low potency (based on guidance values to assist in Category 1 and 2 classification for chronic toxicity; UN, 2007)

Potency	Tumours/Key events
High potency	≤10mg/kg oral, ≤20mg/kg dermal, or inhalation ≤50ppm gas, ≤0.02mg/L vapour, ≤0.02mg/L dust/mist/fume
Low potency	>10mg/kg oral, >20mg/kg dermal, or inhalation >50ppm gas, >0.02mg/L vapour, > 0.02mg/L dust/mist/fume

figure 1.

The ECETOC paper lays out a series of questions (shown in figure 2.) to be applied during the evaluation of data from experiments with rodents; epidemiological data which could lead to Category 1A are not considered in this scheme. Answers to each question can lead either to a classification decision or to the next question.

It is being pointed out that this process should only be implemented in an environment of informed scientific opinion. Detailed guidance is provided on how to address these questions in determining carcinogen classification. It was concluded that mode of action and potency are probably the most important of the above-mentioned factors. The scheme is illustrated with five case studies: thiamethoxam, melamine, dichlorvos, formaldehyde, and Sudan I.

Stepwise approach to the classification of a substance, not otherwise classifiable as Category 1A on the basis of epidemiology, as a carcinogen using the GHS criteria

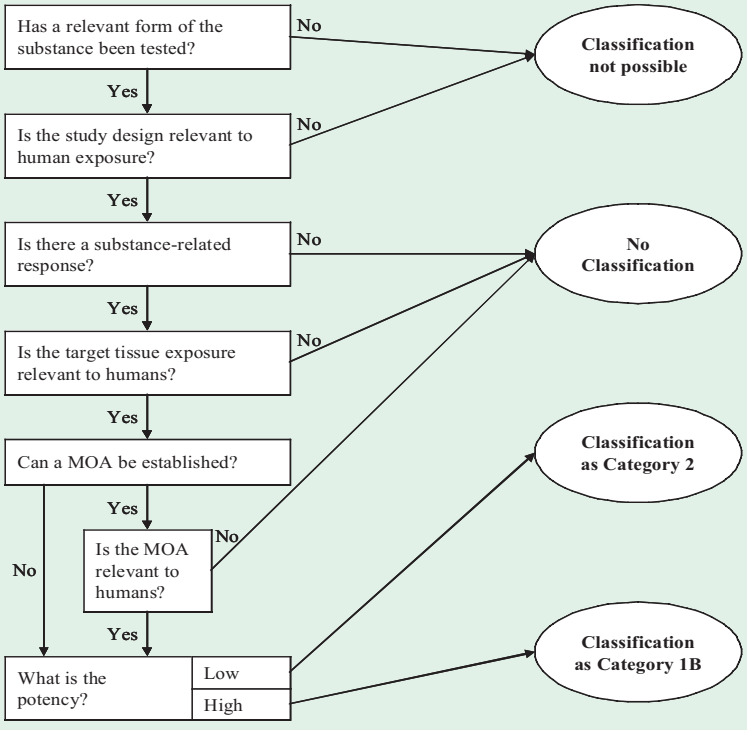

figure 2.

Reference to the ECETOC scheme has been made in the report of the REACH Implementation Project - RIP 3.6 (on the introduction of the GHS guidelines into the new EU chemicals legislation).

The task force presented first concepts for wider input at EUROTOX 2007, at the ECETOC-organised session 'Carcinogen Classification – Moving from a hazard to a risk-based system', and the final scheme at last year's European meeting of the Toxicology Forum.

THRESHOLD OF TOXICOLOGICAL CONCERN PROJECT PRESENTS RESULTS

Strategic Science Area: Intelligent/ integrated testing strategies

The (former) task force on the Threshold of Toxicological Concern (TTC) has successfully finished monitoring the related LRI-funded project 'Use of RepDose for evaluation / refinement of the TTC-concept' that was carried out by the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM). Results were also presented at the EUROTOX 2009 meeting. An overview of established TTC values and those under development has been prepared by the task force and can be downloaded from ECETOC's website.

SUPPORTING THE CEFIC LONG-RANGE RESEARCH INITIATIVE (LRI)

The Cefic Long Range Research Initiative is a strategic research programme to identify and fill gaps in our understanding of the hazards posed by chemicals and to improve the methods available for assessing the associated risks. Since the establishment of the programme in 1998, ECETOC has been a partner organisation. Within the LRI, ECETOC has the responsibility of maintaining three 'core teams' consisting of industry scientists, who manage the scientific evaluation of applications for funding, recommend the best research proposals and monitor of the progress of selected LRI projects.

Human Exposure and Tiered Risk Assessment (HETRA)
In November 2009, the HETRA team assisted by external experts evaluated new proposals for research on 'Indoor environments & risk assessments', and 'Realistic estimation of exposure to substances from multiple sources'. The requests for proposal (RfPs) had resulted from a workshop on consumer exposure. In all, four projects were selected and these were recommended to Cefic-LRI for funding.

Health Effects Monitoring Team (HEMT)
In the last quarter of 2009, the Health Effects Team ran selection committees for the following new projects:
- A toxicogenomic approach to enhance the specificity and predictive value of the murine local lymph node assay
- Towards standardised testing guidelines (reproductive toxicity) relevant to nano materials
- Assessment of risk factors influencing trends in incidence of female breast carcinoma

Environment Monitoring Team (EMT)
In the last quarter of 2009, the Environment Team evaluated the following new proposals for research:
- Rapid estimation of Tiered Methods for Fish (TMF) using laboratory, field and computer modelling methods in aquatic organisms
- Generate a validated Critical Body Burden (CBB) database and validate a CBB chronic toxicity range for narcotics

LATEST Publications

Technical Report No. 107	Addendum to ECETOC Targeted Risk Assessment Technical Report No. 93 (December 2009)
Workshop Report No. 18	Enhancement of the Scientific Process and Transparency of Observational Epidemiology Studies (November 2009)
Workshop Report No. 16 and Addendum	Guidance on Interpreting Endocrine Disrupting Effects (October 2009)

Published Articles:

McGregor et al. 2010. Guidance for the Classification of Carcinogens under GHS. *Crit Rev Toxicol* 40 (3) 245-285.

Loveless et al. 2010. Potency Values From the LLNA: Application to Classification, Labelling and Risk Assessment. *Regul Toxicol Pharmacol* 56, 54-66.*Regulatory Toxicology and Pharmacology* 56, 54-66.

ECETOC In Brief

ECETOC, **E**uropean **C**entre for **E**cotoxicology and **T**oxicology **o**f **C**hemicals, was established in 1978 as a scientific, non-profit, non-commercial association, financed by 46 of the leading companies with interests in the manufacture and use of chemicals. A stand-alone organisation, it was established to provide a scientific forum through which the extensive specialist expertise in the European chemical industry could be harnessed to research, review, assess and publish studies on the ecotoxicology and toxicology of chemicals.

Website

Be sure to visit www.ecetoc.org to download any of our publications

FORTHCOMING Meetings

March

15	Environmental impact assessment for socio-economic analysis of chemicals task force meeting London, United Kingdom
16	Cyanides antidotes 8th task force meeting Darmstadt, Germany
19	Approaches for read-across in chemical risk assessment task force teleconference
22	Linear Polydimethylsiloxanes task force teleconference
25	Assessment Factors to Derive DNELs workshop Barza d'Ispra, Italy

April

14	LRI Health Effects Monitoring Team meeting ECETOC, Brussels, Belgium
22-24	Symposium and Workshop on '*Innovation through Nanotechnology and Nanomaterials – Current Aspects of Safety Assessment and Regulation*' in partnership with the German Toxicology Society Dresden, Germany
28-29	185th Scientific Committee meeting ECETOC, Brussels, Belgium
29-30	Linear Polydimethylsiloxanes 2nd task force meeting ECETOC, Brussels, Belgium

May

23	SETAC Europe 20th Annual meeting Seville, Spain

June

8	Annual General Meeting (AGM) & Annual Technical Meeting (ATM) Bedford hotel, Brussels, Belgium
9	186th Scientific Committee meeting ECETOC, Brussels, Belgium

Next Edition ...
A review of the 2009 ATM and AGM to be published in the summer.

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