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e-NEWSLETTER

EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

No. 14, May 2009

Strategic Science Area: Intelligent Testing Strategies

NEXT GENERATION OF ECETOC TARGETED RISK ASSESSMENT TOOLS

The ECETOC targeted risk assessment (TRA) task force reported in 2004 (Technical Report 93), and launched the supporting web-based tool shortly after. Since 2004, almost 2000 users have registered with ECETOC to gain an access to the tool and benefit from its abilities. As part of the process for maintaining the integrity and relevance of the TRA approach, ECETOC has also held a series of meetings and events with experts from member companies and regulatory authorities with the aim of identifying what further modifications may be either necessary or beneficial.

The TRA Task Force was re-convened in 2006 with the aim of reviewing the current basis for the approach and making recommendations for further improvements. The task force's initial recommendations were delivered to ECETOC's Scientific Committee in 2007 and were subsequently scoped in terms of the work effort required to integrate them into an updated version of the TRA tool. At the same time, the value of the TRA was recognised under the Commission's REACH activity on the developing Technical Guidance for Chemical Safety Assessments (CSAs). Specifically, the TRA has been seen as the preferred approach for evaluating worker health risks (at the Tier 1 level) as well as having the potential for evaluating consumer health risks. At the same time, the need to develop a more workable and pragmatic approach to environmental risk assessment using the principles laid down within the EUSES model was accepted.

Since the summer of 2007, ECETOC has developed the ideas and science underpinning the TRA and continued its dialogue with the Commission/EChA. The TRA task force has therefore worked over recent months to develop improved exposure estimation models for workers, consumer and the environment that carry forward the principles that were pioneered in the original TRA web tool whilst accommodating many helpful suggestions from the stakeholder processes.

The TRA task force held a members' workshop in February to beta-test the revised versions of the 3 exposure estimation models (environment, consumers and workers). Comments and feedback have been incorproated and the final versions have been presented at a fully-subscribed non-member workshop this 15 May.

At this event, ECETOC shared the new tools together with supporting user guides. This non-member workshop presented these key REACH tools that function to support the work of CSA and Exposure Scenario development within Consortia and SIEFs; and explained the rationale and key changes from 2004.

From mid-June, the new models will be available to download from **www.ecetoc.org/tra**
ECETOC will organise an additional workshop to provide interested users with an opportunity to get the most out of the tool if sufficient interest is expressed.

Inside this issue

SG CORNER

This time last year the chemical industry was concerned about the imminent launch of the REACH process. The annual report for the year 2007, placed much emphasis on the forthcoming surge in activity related to this legislation. It was, however, a period of relative optimism about the future. Now, in 2009, with the downturn in world trade, companies have more serious issues, related to short-term results and longer-term survival.

The financial crisis has many aspects which impinge on ECETOC, both directly and indirectly. Firstly, there is our day to day business. For a period, it was very hard to keep task forces on track as many companies had instituted travel bans. During this period, we received the resignations of a few companies which had found themselves forced to make emergency cost cuts. Hopefully, some may reverse that decision if circumstances permit.

Now however, it seems as though the most drastic action has passed and companies are again beginning to look at the longer term. This is reflected in the energy available for ECETOC's activities and some slow moving task forces have started to pick up steam again while new proposals are being submitted to the Scientific Committee.

We have some very interesting new areas in development as I write: our task force on the identification of endocrine disruptors is finishing its report in preparation for an important workshop in June. Meanwhile other workshops are in preparation on subjects such as scientific standards in epidemiology and the use of mode of action in risk assessment.

Coming along sooner than any of these events, will be our Annual Technical Meeting

SG CORNER continued..

(ATM) and Annual General Meeting (AGM). We have deliberately linked these together to encourage participation at both events. The ATM this year aims to encourage younger scientists from member companies to become more involved in ECETOC activities and it will be their ideas that will form the content of the programme, which focuses on the use of new technologies in risk assessment. The material is excitingly varied. A poster session, in the form of a competition, will follow directly on from the AGM and the following day there will be platform sessions and breakout groups. I hope, despite the difficult times, as many of you as possible will attend.

To bring this piece full circle to a more optimistic conclusion, I am happy to announce that a new company has joined ECETOC. Firmenich is the largest privately owned perfume and flavour business in the world and joins our other important members from this sector: Givaudan and IFF.

Another area where we hope to increase membership is the pharmaceutical sector. Already many of the biggest companies in this area are members and we hope to further increase participation. To that end we organised a scoping meeting here in Brussels with an emphasis on environmental issues confronting the pharmaceutical industry. At present there is an increasing emphasis on issues relating to the fate of pharmaceuticals in the environment and an industry approach to the technical issues could be facilitated by ECETOC. The participation from member and non-member companies confirmed that there is need for a science based initiative in this area.

So, there is plenty of activity for ECETOC at the moment. Hopefully the business climate will soon improve and ECETOC looks forward to continued support from all sectors of the chemical industry.

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 to detailed 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 'cardiac sensitisation' report

At its April meeting, the Scientific Committee reviewed a report prepared by the task force on 'cardiac sensitisation' test methods and the report was consequently approved for publication.

Cardiac sensitisation means that the normal heart rhythm becomes perturbed, for example when halogenated or unsubstituted hydrocarbon vapours are inhaled, for a short time, in combination with high internal adrenaline levels (stress). The resulting cardiac arrhythmias may be fatal. Therefore, the cardiac sensitisation potential (and other toxicological properties) of fluorocarbon products needs to be known before those products can be safely used, especially in air-conditioning and fire-fighting applications. Although not a standard regulatory endpoint, the cardiac sensitisation test is a key element in the toxicological assessment of alternative halogenated hydrocarbon products.

The report reviews how cardiac sensitisation studies have been conducted on halogenated hydrocarbons (using the adrenaline-treated dog) and the way in which those test results are used in the prediction of human risk from acute exposure to high concentrations. Critical aspects of the test protocol are the selection of the dose of adrenaline used to 'challenge' the heart, and the definition of a positive response (i.e. cardiac arrhythmia). For risk assessment, i.e. extrapolation of the animal data to humans, no additional safety factors need to be applied. For improved risk assessment, human blood levels of the inhaled compounds can be estimated using biokinetic modelling. While the report discusses various possible alternatives to replace or refine the current dog model, the task force concludes that there is no clear alternative test system at present.

Little is known about the underlying biological mechanism of the cardiac sensitisation effect; cardiac sensitisation following exposure to halogenated hydrocarbons seems to be a complex event that is not fully understood at present. The report includes a summary of a separate paper drafted by one task force member entitled 'Mechanisms involved in cardiac sensitization by volatile anesthetics'. It is published in *Crit Rev Toxicol.*

Input to European Commission Committees' preliminary report on 'use of the threshold of toxicological concern (TTC) approach for the safety assessment of chemical substances'

ECETOC's Scientific Committee has provided comments on the work of the scientific committees of DG SANCO (SCHER, SCCP SCENIHR), i.e. now on the aforementioned report. It was judged that this draft report provides a clear and well-structured review of the principles and use of the TTC. However, the reservation expressed for non-oral routes of exposure are probably overstated for cases when it is clear that relevant data or correction factors for route-route extrapolation can be used. In this respect, the conclusions were considered unsatisfactory from a scientific point of view. The end-use of a chemical should not be the determining factor whether or not the TTC concept is applicable. In all cases, exposure data are necessary for using the TTC approach in a chemical's risk assessment.

The report finishes with a discussion on potential applications of the TTC concept but this is limited to cosmetics. One area that can significantly benefit from the use of TTCs is in the implementation of REACH. New and effective paradigms for risk assessment will have to be tried if the expectations for delivery and reduced animal use are to be realised. ECETOC was active in developing the guidance on information requirements (RIP 3.3.), in which the TTC concept has been specifically mentioned. Therefore, the feedback given to the DG SANCO scientific committees was that this draft report on TTC would benefit in both balance and utility if it could also provide an opinion on the use of TTC in REACH.

Dr. John Doe
Scientific Committee Chairman

NANOMATERIALS AND OECD TEST GUIDELINES

Strategic Science Area: Risk assessment of innovation

This task force was set up to provide input to the OECD 'Working Party on Manufactured Nanomaterials', in particular to the sub-groups that reviewed the OECD test guidelines concerning their suitability for nanomaterials.

The project developed a lot faster than originally expected which was however, for the benefit of the testing of nanomaterial reference materials that has now begun also under the auspices of the OECD and involves many organisations and countries. The task force pulled together specific comments and timely submitted them via BIAC (the official representation of industry at the OECD).

The task force concluded that OECD test guidelines are generally applicable to nanomaterials unless the mentioned test programme on the reference materials would show this differently for a certain nanomaterial or a particular guideline test. Importantly, it was pointed out that the physico-chemical properties of nanomaterials require careful sample preparation for their testing in biological samples (mammalian or eco-toxicological models) and to study environmental fate. The two letters with the specific comments made by the task force are available to members on ECETOC's members' website. The report of the OECD working party is currently being de-classified and soon expected to be available.

Strategic Science Area: Risk, hazard & precaution

POTENCY VALUES FROM THE LOCAL LYMPH NODE ASSAY: APPLICATION TO CLASSIFICATION, LABELLING AND RISK ASSESSMENT

Building on previous ECETOC work, a new task force was started in mid 2007 with the remit to:

- determine whether an EC3[1] potency value derived from the LLNA[2] can be used to provide a cut-off criterion for the classification and labelling of both substances and preparations as a skin sensitiser according to the Globally Harmonised System (GHS) and the Dangerous Substances and Dangerous Preparations Directives, and, if confirmed, develop sub-categories based on EC3 values;
- evaluate the current use of LLNA data in risk assessment approaches for skin sensitisation and propose a rationale for using concentration responses and corresponding no-effect concentrations by taking into account potency considerations.

The report of this task force has been published in December 2008 as Document No. 46.

The conclusion on the first remit is that although skin sensitising chemicals having high EC3 values may represent only relatively low risks for human health, it is currently not possible to define an EC3 value below 100% that would serve as an appropriate threshold for classification and labelling of substances as R43.

The task force also reviewed classification of contact allergens according to relative potency based on LLNA data. Specifically, the task force considered whether, in the light of developments since the original recommendations were made, there is reason now to revise those recommendations. Following these deliberations the task force concluded that the recommendation made previously for four sub-categories of skin sensitisation potency, i.e. 'extreme', 'strong', 'moderate' and 'weak' to reflect differing skin sensitisation potency based on derived EC3 values, is still the most appropriate classification scheme. The corresponding EC3 values are as given in the following table. The recommendations of an expert group of the (former) ECB (European Chemicals Bureau) are also given, although they have, as yet, not been accepted by any regulatory authority. For perspective, also under GHS the binary categorisation of skin sensitisation in the existing legislation remains, with a requirement to only indicate whether a substance is a sensitiser (Category 1) or not.

Proposed potency-based cut-off values for classification of skin sensitising substances

Potency rating	ECETOC	ECB
	Concentration thresholds (%)	Concentration thresholds (%)
Extreme	<0.1	≤0.2
Strong	≥0.1 – <1.0	>0.2 - ≤2.0
Moderate	≥1.0 - <10	>2.0
Weak	≥10	N/A

Concerning classification and labelling of preparations, the task force made recommendations based on the potency of their individual substances, based on their direct testing and based on comparisons with similar preparations. For the first of these, which is likely the most common case, a proposal was made for potency-based cut-off values; the values are given in the next table. Applying those would provide improved classification and labelling compared with what is currently required by the Dangerous Preparations Directive and its amendment. According to the latter, a level of ≥1% of a skin sensitiser ingredient requires a hazard categorisation of the preparation as a skin sensitiser, irrespective of potency. For a quantity of ≥0.1% but <1%, the skin sensitising substance has to be declared on the label, even though the preparation is not classified as sensitising.

Proposed potency-based cut-off values for classification and labelling of preparations

Potency	Sub-category	Concentration limit of sensitising ingredient present in solid and liquid preparation (% w/v)
Extreme	1a	0.003
Strong	1b	0.1
Moderate	1c	1.0
Weak	1d	3.0

To address the second remit, the task force reviewed recently published approaches for quantitative risk assessment of skin sensitising chemicals based on the relationship between the calculated exposure to a sensitising chemical and the acceptable exposure level. The first step in the quantitative risk assessment process is to establish a NESIL[3]. The task force concluded that EC3 values derived from the LLNA are well suited for the determination of a NESIL because the proliferation of cells in draining lymph nodes is related causally and quantitatively to the extent to which skin sensitisation will be acquired (potency).

With these recommendations regarding the use of potency considerations based on EC3 values, the LLNA is not only a component of hazard identification but can also be considered a key component of risk assessment.

[1] effective concentration for a stimulation index of 3 in proliferation of lymph node cells; [2] local lymph node assay; [3] no expected sensitisation induction level

TRIGGERING/WAIVING CRITERIA FOR THE EXTENDED ONE-GENERATION REPRODUCTION TOXICITY STUDY

Strategic Science Area: Reproductive health

Strategic Science Area: Intelligent/ integrated testing strategies

As a follow-up to the task force and workshop on triggering/waiving criteria for the extended one-generation reproduction toxicity study, the task force has written a paper highlighting the conclusions of both activities.

The paper was submitted to *Alternatives to Laboratory Animals (ATLA)* and, upon addressing a few comments from their peer-review panel, accepted for publication. It has appeared in the April 2009 volume of *ATLA* (Vol.37, 219-225, 2009) as another contribution of ECETOC to the development of this OECD test guideline.

ECETOC'S WORLD HEALTH ORGANISATION NGO STATUS RE-CONFIRMED

ECETOC is pleased to announce that its status as an officially recognised non-governmental organisation (NGO) with the World Health Organisation has been extended for another three years.

ECETOC cooperates closely with WHO (International Programme on Chemical Safety - IPCS) on several projects. For example John Doe, Scientific Committee Chairman represents ECETOC as a member of the IPCS Steering Committee on the Harmonisation of Approaches to the Assessment of Risk from Exposure to Chemicals.

LATEST Publications

Technical Report 104	Framework for the Integration of Human and Animal Data in Chemical Risk Assessment (published January 2009)
Document 46	Potency Values from the Local Lymph Node Assay: Application to Classification, Labelling and Risk Assessment (published December 2008)
Workshop Report 15	Workshop on the Probabilistic Approaches for Marine Hazard Assessment (published December 2008)
Technical Report 103	Toxicity of Possible Impurities and By-products in Fluorocarbon Products (published December 2008)

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 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 download any of our publications

FORTHCOMING Meetings

May

21	Environmental impact assessment for socio-economic analysis of chemicals: Practical guidance based on case studies London, United Kingdom
27-28	Interpreting endocrine disrupting effects task force meeting Frankfurt, Germany

June

9	Board meeting (morning) Bedford hotel, Brussels
9	Annual General Meeting (AGM) (afternoon) Bedford hotel, Brussels
10	Annual Technical Meeting (ATM) Bedford hotel, Brussels
12	Risk assessment approaches for PBT/vPvB chemicals or persistent organic pollutants (POP) - 2nd meeting ECETOC, Brussels
15-16	Linear Polydimethylsiloxanes - 2nd meeting ECETOC, Brussels
16	Dermal Risk task force presentation at OEESC (Occupational and Environmental Exposure of Skin to Chemicals) Conference Edinburgh, Scotland
24	Cyanides Antidotes - 6th meeting ECETOC Offices, Brussels
25	Scientific Committee meeting ECETOC Offices, Brussels
26	Guidance for Assessment Factors to Derive DNELs - 1st meeting ECETOC Offices, Brussels
29-30	Guidance on interpreting endocrine disrupting effects workshop Barcelona, Spain

August

21	ECETOC-EEMS Symposium at ICEM 'Nano(geno)toxicology' Firenze, Italy
30-1	2009 World Conference on Alternatives & Animal Use in the Life Sciences: Session on *Chemicals and Pesticides* to be chaired by Neil Carmichael, ECETOC Secretary General Rome, Italy

September

11	Risk assessment approaches for PBT/vPvB chemicals or persistent organic pollutants (POP) - 3rd meeting ECETOC, Brussels
24	Observational epidemiology studies workshop London, United Kingdom

Next Edition ...

We will provide details on developments in ECETOC's environment programme

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