



Australasian College of Toxicology and Risk Assessment

September 2010 E- Newsletter

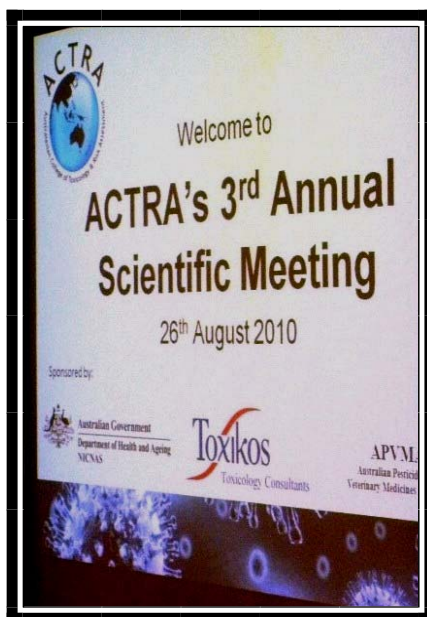
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Members Newsletter

ACTRA 2010 Scientific Meeting & AGM

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The 3rd Scientific Meeting of the Australasian College of Toxicology and Risk Assessment was held on Thursday 26th August at the University of NSW CBD Campus, at Level 6 of 1 O'Connell St, Sydney.

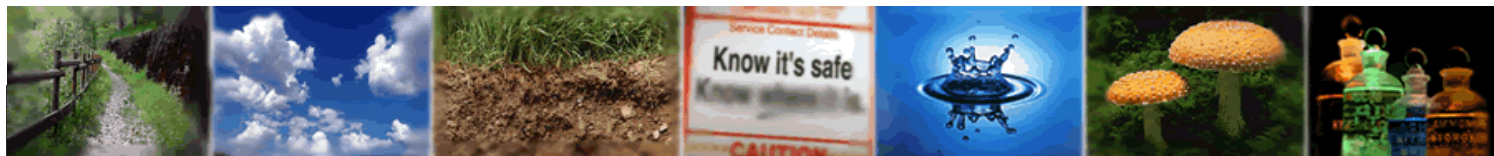
ACTRA members and non-members presented their own research and experience in a stimulating scientific program. The meeting also offered participants a good opportunity to network.

Presidents Report

Welcome to the second ACTRA newsletter for 2010, including details of some forthcoming events that you should note in your diaries.



Thanks are due to Jackie Wright and Elisabeth Dank for arranging a stimulating scientific program and a convenient and well-suited Sydney venue for this important meeting on ACTRA's annual calendar. I would also like to thank sponsors who generously supported the 2010 ASM (NICNAS, Toxikos Pty Ltd and the APVMA). The theme for the scientific program focussed on "moving forward" (to coin an over-used political phrase) in relation to assessing the toxicity of environmental chemicals. Unfortunately, the keynote speaker (Carolyn Vickers, a team leader with the International Programme on Chemical Safety (IPCS) with the World Health Organisation) was a late withdrawal from the meeting, caused by a death in the family. On behalf of ACTRA, I extended condolences to Carolyn on her tragic loss. I was able to alter my own presentation to pick up some of the forward-looking IPCS programs in risk assessment that she would have presented, particularly those aiming for harmonisation of international approaches to HRA.



John Frangos also stepped in as a late replacement with a presentation on looming changes in cosmetics regulation around the world. On the same theme, there was a session on Quantitative Structure-Activity Relationship (QSAR) assessment, featuring an informative talk by a local QSAR expert (Dave Winkler, CSIRO). Since QSAR is becoming an increasingly important tool for prioritising the assessment of chemicals for which there is little or no toxicity data, this session was sponsored by NICNAS, as part of a program developing QSAR as a regulatory tool. Julija Filipovska outlined how NICNAS is co-operating with other regulators in using QSAR to prioritise AICS chemicals for further assessment.

I must express some personal disappointment that the level of interest in ACTRA members submitting free contributions to the scientific program was not maintained from the high level set in 2009. While the quality of the papers submitted in 2010 was again at a high standard, and the feedback from those attending attested to their interest value, the relatively low number of contributed papers caused a late planning change to restrict the ASM to a single day this year. I hope that the 2010 response to the call for contributed papers is a one-off aberration; otherwise the committee will need to consider the wisdom of continuing to contribute the time and resources to arranging such meetings. However, I was more encouraged that the ASM attracted a relatively healthy number of registrants, including some non-members who were exposed to the type of high-class scientific presentations that ACTRA can offer.

ACTRA Workshops and Symposia

I had noted in the June e-Newsletter the outstanding success of the May 2010 **Workshop on Assessment of Carcinogenic Risk**. The number of registrants at that Workshop and the feedback received on the quality of the scientific program was indeed heartening. Elisabethe is currently investigating options for making available to members the copies of the presentations at that workshop, for the benefit of members who may have missed the sessions.

However, I would comment once again that the level of registrations by ACTRA members was not as strong as I would have expected. While I appreciate that there are many claims on members' resources and the current financial and business climate makes it difficult to commit to many training activities, I would remind members that one of the driving forces for the establishment of ACTRA was a recognised deficiency in the number of continuing education activities. While it is great that many non-members are attracted to ACTRA training programs, and get exposed to interesting material in toxicology and risk assessment, the main purpose ACTRA has in running these programs is to benefit members.

I am hopeful that the next ACTRA Symposium, scheduled to be held at the Adelaide Convention Centre on 15 September, will attract a larger number of ACTRA member registrants. The theme of the symposium will be the management of environmental health risks and liabilities. It will feature several talks that address the regulatory approaches to site contamination and water quality, including discussion

of the legal responsibilities and liabilities that might be incurred. Links to the Workshop can be found on page 6.

Forward Planning

At the last committee meeting, I committed to preparing a strategic planning document to assist with planning future ACTRA activities. I invite members to contact me with any thoughts on forward planning or the implementation of the registration program. I am sure the committee will welcome any constructive contributions or offers of assistance with these important matters.

I am also mindful that the implementation of the Registration Program has been slow, given that this is one of the major strategies for promoting professional development and recognising achievements of ACTRA members. The Registration Tribunal is in place and is eager to get on with their work. It includes a number of eminent national and international toxicologists willing to peer review applications for registration. The matters remaining to be resolved by the committee are further development of the format of the applications process and structuring the ACTRA website to facilitate the listing of registrants, along with relevant information about their expertise.

Finally, my term as the inaugural President of ACTRA comes to an end at the next (2011) AGM. I look forward to working with the incoming committee over the next year and I also look forward to the continuing commitment of the membership to help us to achieve the lofty objectives set down when ACTRA was first established.

Brian Priestly—President



from the Editor

Welcome to the *new look* newsletter. Once upon a time I dabbled in design and every now and then I lust to get in touch with my creative side again. The truth be known I was never every good at it but what the heck; this newsletter belongs to you and you will, no doubt let ACTRA know if you like the new format. I expect the style, feel and content to evolve over time. The newsletter has two editors me and John Frangos and we take turns compiling the content. This time its my turn and this is my style; so if you'd like to praise, condemn or contribute please do so directly to me mirella.goetzmann@health.wa.gov.au , ACTRA secretariat@actra.org.au or John johnfrangos@toxikos.com

I have introduced the Opinion piece in this edition and I hope that it will be taken up in subsequent editions. At first I thought it might be by invitation only but then I reconsidered—it could be interesting to open it up to members and non-members alike just to see what emerges. Have a think about it.

The annual ACTRA scientific meeting this year didn't generate the level of interest that we hoped but it was by no means a fizzle. Overall goodwill prevailed and the response from the attendees was very positive. The topics that were covered ranged from the theoretical to the practical. Prof. John Edwards' talk on 'Communities at Risk-Methamphetamines Laboratories in Urban Settings' provided some memorable visuals of the hazards clandestine drug labs pose to neighbours, children found on premises and emergency responders. Read an outline of Johns talk on page 6.

Congratulations to the New ACTRA committee members elected during the concurrent Annual General Meeting —Stay tuned to the website and the next newsletter for the minutes of the meeting.

Society of Toxicology (SOT) and AstraZeneca travel fellowship

Once again, the Society of Toxicology (SOT) and AstraZeneca are very generously sponsoring nine \$2,000 travel fellowships for scientists to attend the SOT Annual Meeting in Washington, D.C., USA (March 6–10, 2011). Applicants may be either junior or senior scientists, reside in countries where toxicology is underrepresented, and have an active research program or currently be active in the practice of toxicology. Please click http://www.iutox.org/AstraZeneca_app.pdf to view a flyer and application with eligibility requirements. Applications are due by October 8, 2010, and awardees will be announced in November. Since IUTOX is administering this awards program, candidates may direct their questions to iutoxhq@iutox.org

International Congress of Toxicology IUTOX Early Toxicologist Award:

The purpose of the IUTOX Early Toxicologist Award is to recognize and stimulate outstanding research in toxicology by newly established investigators. The Award consists of a plaque and reimbursement of the travel expenses incurred to attend the International Congress of Toxicology (ICT); the Award is presented once every three years, at the ICT meeting.

The 2010 Early Toxicologist Award Winner is Geoff Isbister, Australia

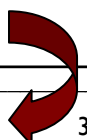
Associate Professor Geoffrey Isbister is a Senior Research Academic at the University of Newcastle School of Medicine and Public Health. His primary area of research is venomous bits and stings, particularly snakes and spiders.

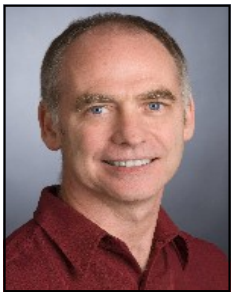
GET READY GET INVOLVED

Take Part in the

2011 ACTRA Scientific Meeting

Register with the
Secretariat to be
kept informed





Opinion:

Thoughts while travelling...John Edwards. 7 September 2010

I received an email from Mirella asking me to write the first of these informal opinion pieces for ACTRA, with a submission deadline of 13 September. Being overseas until the 22 September seemed at first to be a disadvantage, but then I reconsidered. After all, I am overseas on business, attending the 8th International Symposium on Biological Monitoring in Occupational and Environmental Health (8th ISBM) so I should still be able to squeeze in those other work tasks, right? In particular, I can share with you my thoughts of the moment, just after lunch on day 2 of the conference on a balmy Finnish afternoon with a view across Linholmsfjarden at Espoo.

Biological monitoring, as a tool in exposure evaluation and risk assessment, and biological effect monitoring, as an approach to measuring outcomes following exposure to various stressors, are both very under-used in Australia. There have been occasions when research projects that include such strategies have been rejected or modified by funding agencies, government organisations and industries, apparently from a fear of finding out something that may (a) cause workers/investors/authorities to ask questions about exposures and their effects, (b) lead to claims for compensation or other action, or (c) lead to adverse publicity in some way. I believe this is a very short-sighted view and has resulted in poor understanding of the uses and advantages of biological monitoring as a valuable tool in risk assessment. This in turn results in misunderstanding and suspicion about the aims of biological monitoring and the motivation of those of us who practice it. So we see the classic vicious circle develop.

In Europe, the Americas, and elsewhere biological monitoring is embraced, with whole departments at Universities devoted to research and professional practice using it. Enormous research projects in industry and environmental settings are not unusual, and biological monitoring tools are regarded as essential in many epidemiological studies. Industries and businesses *request* biological monitoring studies to assist them in managing workplace chemical exposures. This disparity in views is difficult to fathom and it could be a topic of an ACTRA meeting in the future.

Attending this conference has always been a pleasure (I have missed only one since they began) and the enthusiasm of the 230+ delegates, including a significant proportion of young researchers seeing this as a viable career path, is breathtaking. Papers this week include using mathematical models of chemical exposure and effect, descriptions of emerging hazards for which health risk assessments are being developed, along with the bread-and-butter reports of biological monitoring applied to various exposures. My roles on the International Organising Committee for this conference, and as a Chairperson of a scientific session seem quite disproportionate as I am the only Australian here. Indeed, I was asked on the first day whether I would be able to organise either the 2013 or 2015 conference in Australia. It seems a little incongruous considering my comments here, but I think it would be a great opportunity to both promote biological monitoring within Australia and to promote Australia and our skills in risk assessment to the world. I will be discussing this potential with ACTRA and other organisations in the near future, so who knows? In 5 years we may see ourselves at the centre of a revolution in risk assessment in Australia.



QSAR: what it is, what it can do, and what it can't do

It is clearly necessary to ensure that industrial chemicals used in the home and workplace are not likely to be a significant risk to human health or the environment. Government regulatory bodies have responsibility to ensure that sufficient information is available for new and existing chemical so that hazard and risk can be assessed, and suitable controls can be put in place to manage risk. Experimentally measured physicochemical, toxicological, and environmental impact data has been the main source of information requested and provided for chemical registration process. Experimental measurements also constitute the 'gold standard' against which other sources of data are measured.

A number of technological and regulatory issues have arisen that have put pressure on the ability to rely entirely on experimentally determined data when making decisions on regulation of industrial chemicals. One of these is the cost of generating the required experimental data for registration. This acts as a disincentive to introduce new, more effective and less toxic chemicals to replace those already registered.

It also makes it very difficult for companies to register new chemicals with low value and production volume, as the cost of registration cannot be recouped. There is increasing pressure to curb the use of animals to provide data on toxic effects of chemicals. On the positive side, technological advances are making the cost of some biological assays cheaper because they can be miniaturized and done using high throughput methods, and the availability of gene expression profiling methods promises to provide large amounts of data on how chemicals interact with organisms. Potentially large volumes of data may be generated in the future, and this must be managed and information extracted.

Consequently, all regulatory agencies have started investigating and, in some cases, using computational methods to predict physicochemical or toxicological properties of chemicals. Foremost of these are the quantitative structure-activity relationships (QSAR) methods.

These are machine learning or regression techniques that extract information on the relationships between the molecular or physicochemical properties of molecules and their biological properties. QSAR was developed about fifty years ago and has been invaluable for drug development and prediction of physicochemical properties of molecules. It can make accurate prediction of properties of complex toxicological properties in some cases, and is excellent at analyzing large data sets in particular. Most agencies are interested in the potential of QSAR methods for predicting toxicological properties of chemicals, and for prioritizing inventories of existing chemicals in terms of hazard and risk.

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[See the last page](#)

**Highlights from the
ACTRA
Scientific Meeting
in Sydney
Spot
the Toxicologist**

Communities at Risk—Methamphetamine Laboratories in Urban Settings

Illegal drug laboratories clearly pose a risk to health of those with direct contact with the premises where drug manufacture takes place. These include the cooks themselves, their families and other residents of the premises, first responders including police, fire and ambulance personnel, and any contractors involved in the remediation of the premises. However, depending on the nature and quantity of chemicals used and produced, their location within the laboratory, the emission or discharge of chemicals from the premises, and the proximity of nearby buildings and other members of the community, there may be significant risks to others not closely associated with illegal drug manufacture. This presentation explored issues involving the prevalence of illegal drug laboratories in the community, their potential locations and the health risks they may represent to communities.

Nanotechnology Work Health and Safety Symposium

9 Sep 2010 - 10 Sep 2010. Theatrette, Parliament House, Canberra

Safe Work Australia and the Department of Innovation, Industry, Science and Research held a symposium on Nanotechnology Work Health and Safety Symposium.

This symposium presented findings of research projects on engineered nanomaterials, with focus on possible exposure risks and effective prevention methods to control exposure to nanomaterials.

The symposium brought together a broad range of delegates including researchers, industry and union stakeholders and representatives from work health and safety regulatory authorities.

The symposium featured presentations by the ACTRA members. Roger Drew on the toxicology and health effects of engineered nanomaterials. John Frangos presented two papers on; safety hazards of engineered nanomaterials and a survey of engineered nanomaterial Material Safety Data Sheets and Labelling. Several sessions were chaired by Brian Priestly.

Megan Osmond from the CSIRO presented an interesting paper on the durability of carbon nanotubes and potential inflammation and Mark Horsam of NICNAS presented a hazardous substance classification for carbon nanotubes.

Safe work Australia in particular Dr Howard Morris should be congratulated on organising a robust symposium on this important issue. The symposium was a summary of the research conducted over the past few years under the Nanotechnology OHS Program. The program focused on understanding:

- Possible effects that engineered nanoparticles might have on human health
- Potential exposure in the occupational use of engineered nanomaterials
- Effective prevention of occupational exposure to engineered nanoparticles

The research reports can be found at

<http://www.safeworkaustralia.gov.au/swa/HealthSafety/EmergingIssues/Nanotechnology/>

John Frangos



Regs Corner

Tuesday 31 August, 2010

The New Zealand Department of Health has released Guidelines for the Remediation of Clandestine Methamphetamine Laboratory Sites.

Electronic copies of the guidelines are available on the Ministry of Health website at:

<http://www.moh.govt.nz/moh.nsf/indexmh/guidelines-remediation-clandestine-meth-lab-sites>

The Annapolis Accords on The Use of Toxicology in Risk Assessment and Decision-Making

Introduction

The science of toxicology plays an important role in identifying safe conditions of use or exposure for many different kinds of environmental agents. The use of toxicological information in risk assessment requires careful analysis, evaluation of data, and scientific judgment. A team of experts co-sponsored by The American College of Clinical Pharmacology and The Society of Toxicology under the chairmanship of Dr George Gray (Director of Food Safety & Agriculture, Harvard Centre for Risk Analysis, Harvard School of Public Health) have come up with "The Annapolis Accords on The Use of Toxicology in Risk Assessment and Decision-Making".

The Accord addresses a range of issues that we face as toxicologists and health risk assessors and provides solutions, which may help to manage them. The Annapolis Accords are intended to guide appropriate use in risk assessment of the scientific information from toxicology. It is advocated that the application of the principles defined in the Accord will improve the scientific credibility of risk assessment and the quality of decisions aimed at reducing and eliminating risks to human health and the environment.

A summary of the Annapolis Accord is given below and the full document can be obtained from the site:

<https://www.accp1.org/pdf/papers/Toxicology.pdf>

It is hoped that the Accords will serve as guideposts for the purposes of evaluating the strengths and weaknesses of past risk analyses in our part of the world, and of improving the quality of future analyses.

The Annapolis Accord

"Annapolis Accords for the Use of Toxicology in Decision-Making"

- 1. Toxicology provides reliable, relevant, and objective scientific information that should be used in efforts to assess and compare health and environmental risks, to identify risk reduction opportunities, and to reduce uncertainty.**

Toxicology is a discipline applying the methods of science that is used to protect human and environmental health. The science of toxicology has demonstrated that all agents are not alike; substances vary markedly among one another in the amount of exposure necessary to cause biological effects, in the nature and severity of the effects generated, and in the specific circumstances of exposure under which they may constitute hazards. Such information is directly useful in risk assessment, risk management, and basic toxicologic research. Through risk assessment, toxicologic information enhances understanding of the source, magnitude, and likelihood of risks.

There is concern in the public health community that personal and social decisions often focus on risks of minor biological significance while ignoring risks of greater, biologic significance. For example, small risks that may possibly be posed by pesticide residues in foods have produced considerable consumer concern, while more substantial and more certain risk to ill health caused by poor nutrition and unbalanced diets have received less attention.

The scientific information developed by toxicologists has important uses in social decisions about risks from physical, chemical, or biological agents. If used properly and systematically, toxicologic information can help decision-makers, legislators, journalists, and the public understand the relative magnitude of different risks. Toxicologic research also can help identify methods of risk reduction, thereby decreasing the uncertainties associated with risk assessment.

- 2. Toxicologic research seeks to define the conditions of exposure to physical, chemical, or microbial agents that do not produce adverse effects. Attainment of this goal requires the best available characterization of intensity (dose), duration, frequency, and route of exposure.**

The Annapolis Accords on The Use of Toxicology in Risk Assessment and Decision-Making *con't*

A fundamental tenet of toxicology is that the dose makes the poison. Consequently, sound assessment of safety requires knowledge of the conditions of exposure, especially the intensity, duration and frequency of exposure. Numerous toxicologic studies have demonstrated that similar intensities (doses) of exposure to an environmental¹ agent can have widely different effects depending on duration and frequency. Proper use of toxicologic information in risk assessment should, insofar as possible, match exposure information to the known toxicologic determinants of response.

3. Differences in factors potentially influencing toxicologic susceptibility among people should be considered relevant to a risk assessment if those factors have been demonstrated to influence target organ toxicity, clinical disease, or objectively verifiable biochemical abnormalities.

Advances in understanding of genetic differences among people have occurred amidst public interest in potential variation in human susceptibility to various health hazards. This Accord addresses the concern that identifiable genetic differences among people might be inappropriately interpreted as differences in risk. Importantly, potential sources of variation are not always toxicologically relevant at expected conditions of exposure.

As more information about genetic variability and susceptibility becomes available, it is critical that data about intensity, duration, and frequency of exposure be considered in any quantitative assessment of risk.

Differences among people can be irrelevant at some doses but may be relevant at others.

The relationship will rarely be proportional to measurable differences in biomarkers such as enzymatic rates or protein function. The differences will be chemical- and effect-specific use of this type of toxicologic information in risk assessment should occur only when the differences have been demonstrated to be relevant for toxic effects at expected exposure levels.

4. In order to be useful for assessing health outcomes, biomarker determinations must accurately predict target organ toxicity, clinical disease, or biological abnormalities. Biomarkers of exposure should not be used as predictors of adverse effects if no such relationship has been or can be shown.

The development of biomarkers as indicators of exposure to a toxic agent or of induction of adverse effects in individuals or populations enhances a closer collaboration between exposure assessment and toxicology. Biomarkers have promise for increasing knowledge of dose-response relationships for risk assessment; however, invalidated biomarkers can potentially be misused.

The relationship between a biomarker and an endpoint of concern must be established. Biomarkers of exposure (*e.g.*, protein adducts) should not be used as markers of toxicity unless specific data have been developed that quantitatively link the marker to disease or toxicity.

Biomarkers of toxicity also must be validated for their predictive power and quantitative relationship to a specific adverse effect. Biomarkers are potentially powerful toxicologic tools for risk assessment, but appropriate application requires an understanding of the nature of a marker and validation of its association with toxicity or illness.

5. Plausible alternative interpretations of exposure and toxicologic information underlying a risk assessment should be articulated. The extent of scientific consensus associated with those interpretations should be characterized.

Risk assessment necessarily requires assumptions and choices when using toxicologic information. The need to make decisions before scientific certainty can be established, if indeed it can be established, means there will be uncertainty in the use of toxicology information for risk assessment. Alternative choices and assumptions can have very different implications for judgments about risk. To provide decision-makers with an accurate characterization of a situation, all scientifically plausible estimates of risk should be articulated and the scientific differences among them identified. The judgment of toxicologists should be used to guide identification of the most scientifically valid interpretations.

Cont'd

6. Toxicologic research in animals can improve understanding of potential hazards to human health. Characterization of animal evidence in assessment of human health risk should consider the weight of the evidence for a particular effect and its relevance to humans.

Toxicologic research often relies upon studies of animals to characterize and extrapolate the potential effect of substances on humans and other species. The need to generalize effects across species and to extrapolate to different exposure conditions requires judgment in evaluating toxic effects and their relevance to other species. Confidence in judgments about the interspecies relevance and reliability of animal toxicity data is enhanced

when the following issues are explicitly addressed.

- Rigor – Studies should be evaluated for their proper conduct and analysis. Greater weight should be given to more rigorous studies. Some studies may have been performed so poorly that their results should be discounted.
- Power – The statistical power of an experimental design should be examined for its ability to detect effects of a given magnitude. For example, in some "negative" studies, a low level of response could be misinterpreted as a lack of response.
- Corroboration – When specific effects are replicated in similar studies, or similar effects are seen under varied conditions, decision-makers can be confident that effects would be seen under conditions of human exposure as well. Conversely, lack of corroboration provides a basis for doubting either the validity of single experimental results or their applicability to other species or conditions of exposure.
- Universality – When valid testing reproduces an effect in multiple species by various routes of exposure, decision-makers can be more confident that the effect may apply to humans. By contrast, if an effect is restricted to a certain species, strain, or route of administration, there is less confidence in the ability to generalize the response to other species or routes.
- Proximity – When effects have been shown in a species taxonomically related to humans or at doses similar to those expected in humans, such results weigh more heavily than effects found in taxonomically less related species by less relevant routes, or at markedly different dosages.
- Relevance – From knowledge of the underlying biologic basis for a toxic response in animals, experts and decision-makers can assess whether similar metabolism, mechanisms of damage and repair, and molecular targets of toxic action should be expected to operate in humans. Accordingly, confidence in applicability to humans can increase or decrease.

- Cohesion – The extent to which all of the data are consistent and are subject to a single biologically plausible explanation increases weight of evidence when compared to situations where inconsistencies require *ad hoc* explanations and exceptions to general patterns.

These themes, while not entirely distinct, identify key elements of information and judgment that contribute to valid assessment of the weight of evidence used to decide if an effect seen in animal studies should be regarded as a potential risk in exposed humans. If a more operational scheme is needed, it may be necessary to codify the judgments into rules about what elements of evidence will lead to acceptance of an effect as sufficiently established to pose a risk to human health. Rigid rules for interpretation of scientific evidence however, can work against the exercise of good judgment. Consequently, consensus criteria should not be followed blindly if evaluation of the considerations listed above suggests that doing so would be misleading."

Dr Ram Sharma & Sally McKinnon,
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Membership Reminder

If you haven't already done so, please renew your ACTRA membership. Renewal can be done on line:

www.actra.org.au

New Members

ACTRA Welcomes

Judith	Cox	PAEHolmes
Judith	Barnes	Golder Associates
Janith	Wickramaratna	NICNAS
Stephen	Batt	Office of Chemical Safety & Environmental Health
Therese	Manning	NSW DECCW
Toh Ming (James)	Ngu	Geotechnique Pty Ltd
Adam	Capon	NSW Health
Graham	Ohmsen	Environmental Resources Management Australia (ERM)
Gemma	Williams	AECOM

Contributions by individual members and opinions expressed within these contributions are not intended to nor do they represent the views of the Australasian College of Toxicology and Risk Assessment.

In the Journals

Rothfuss, A., et. al. (2010) *Collaborative study on fifteen compounds in the rat-liver Comet assay integrated into 2- and 4-week repeat-dose studies*. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, v 702 (1), 40-69.

One of the themes at recent ACTRA Annual Scientific Meetings has been toxicity testing in the 21st century. There is a current shift in paradigm towards integration of testing to reduce the number of animals used in testing without compromising the hazard identification process. An example of this is the integration of genotoxicity endpoints in repeat-dose toxicity studies, e.g., the 28-day rat-toxicity study.

Recently proposed guidance on the requirements for genotoxicity testing of pharmaceuticals and chemicals encourage such an integration of genotoxicity tests into repeat-dose toxicity studies, whenever possible and scientifically justified (ICH 2010, ECHA 2009).

The in vivo Comet assay (single-cell gel electrophoresis assay) is increasingly used in regulatory genotoxicity testing for the evaluation of DNA damage and repair in various tissues of mice and rats. Besides the obvious contribution to the reduction of animal use in genetic toxicology, an integrated measurement of genotoxicity endpoints also offers the possibility for an improved genotoxicity risk assessment, since such data will be evaluated in conjunction with routine toxicological information obtained in the repeat-dose toxicity study, such as haematology, clinical chemistry, histopathology and exposure data.

To evaluate whether the liver Comet assay is suitable for integration into repeat-dose toxicity studies in the rat, a collaborative study was performed, involving 14 laboratories from Europe, Japan and the USA.

Male rats received oral administrations of the test compounds, daily for two or four weeks. The top dose was meant to be the highest dose producing clinical signs or histopathological effects without causing mortality, i.e. the 28-day maximum tolerated dose. The liver Comet assay was performed according to published recommendations and following the protocol for the ongoing JaCVAM validation trial. Laboratories provided liver Comet assay data obtained at the end of the long-term (2- or 4-week) studies together with an evaluation of liver histology. Most of the test compounds were also investigated in the liver Comet assay after short-term (1–3 daily) administration to compare the sensitivity of the two study designs.

MN analyses were conducted in bone marrow or peripheral blood for most of the compounds to determine whether the liver Comet assay could complement the MN assay for the detection of genotoxins after long-term treatment.

The article provides a detailed description of the tests conducted and the outcomes for each of the 15 test chemicals utilised (Benzo[a]pyrene, 1,2-Dimethylhydrazine dihydrochloride, 2,6-Dinitrotoluene, Dimethylnitrosamine, 1,2-Dibromoethane, 2-Amino-3-methylimidazo[4,5-f]quinoline, 2,4-Diaminotoluene, 2,6-Diaminotoluene, Acrylamide, Chlorodiazepoxide, Pyrimethamine, Gemifloxacin mesylate, Methapyrilene, Clofibrate, Phenobarbital). A comparison of the previous results and the present study results is also provided.

The conclusions of the collaborative study were supportive of the integrated into repeat-dose toxicity studies over 2–4 weeks. Except for the “difficult” pair 2,4- & 2,6- diaminotoluene, all of the known liver-specific genotoxins gave the expected positive Comet-assay result when tested up to the 28-day MTD. The three non-genotoxic carcinogens were all negative in the Comet assay after long-term treatment, despite clear liver toxicities observed by histopathology, suggesting that moderate necrosis, hyperplasia or inflammation do not lead to (false) positive Comet assay results in the liver.

References

ICH S2(R1) Genotoxicity: Testing and Data Interpretation for Pharmaceuticals Intended for Human Use, Step 2 Document, 2008,

<http://www.ich.org/LOB/media/MEDIA4474.pdf>

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ECHA (2009) Guidance on information requirements and chemical safety assessment, Ch. R.7a: Endpoint Specific Guidance. See chapter R.7.7.1 Mutagenicity Testing, 374-402, ECHA publication on Information requirements R7a.

John Frangos

EVENTS CALENDAR

Managing Environmental Health & Liabilities	September 15, 2010	Adelaide www.actra.org.au/news.html
Genetic Toxicology in the 21 st Century: The Scientific Basis for New Technologies and Regulatory Guidance	September 15–16, 2010	John M. Clayton Hall Conference Centre, University of Delaware, Newark, Delaware www.gta-us.org/
The fifth annual conference of the Society for Risk Analysis - Australia and New Zealand	September 27-29, 2010	University of Sydney www.acera.unimelb.edu.au/sra/news.html
Better Air Quality 2010 - Air Quality in a Changing Climate	9-11 November, 2010	Singapore www.cai-asia.org
National Short Courses in Environmental Health	18th November to 1st December 2010	Flinders University ADELAIDE www.nsceh.com
28th Annual AIOH Conference and Exhibition	4-8 December, 2010	Hobart www.aioh.org.au
Int. Conference on Biology, Environment and Chemistry (ICBEC 2010)	28-30 December, 2010	Hong Kong www.icbec.org/
SOT 50th Annual Meeting	March 6–10, 2011	Washington Convention Centre Washington, DC www.toxicology.org
Indoor Air 2011	5 -10 June, 2011	Austin, Texas http://lifelong.engr.utexas.edu/2011/
20th Int. Clean Air and Environment Conference	5 - 8 July, 2011	Christchurch www.casanz.org.au
EUROTOX 2011	August 28–31, 2011	Paris, France www.eurotox.com

after hours

Worries about Risk

There is a story about a monastery in Europe perched high on a cliff several hundred feet in the air.

The only way to reach the monastery was to be suspended in a basket which was pulled to the top by several monks who pulled and tugged with all their strength.

Obviously the ride up the steep cliff in that basket was terrifying. One tourist got exceedingly nervous about half-way up as he noticed that the rope by which he was suspended was old and frayed.

With a trembling voice he asked the monk who was riding with him in the basket how often they changed the rope. The monk thought for a moment and answered brusquely, "Whenever it breaks."



Publication of any material submitted to the ACTRA Newsletter will be the sole discretion of ACTRA.

ACTRA reserves the right to make amendments to the submission prior to publication, or to refuse publication.

QUIZ WOT THE ?



Members please share with us any news about yourself. We would like to hear about awards, grants, collaborations, moves, promotions, interviews, journal/book reviews, jokes, stories, positions vacant and ideas for new items.

How do you like the new format of the newsletter?

Please let us know how the hyperlinks are working. If things look a little awry we'll get better I promise.

Thank you - The Editors

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'Step Up, Step Up, Get your miraculous elixir, eliminate disease', cried the snake oil salesman.

The salesman asked a man from the front row of the gathering crowd to blow through a straw into a glass of clear liquid labelled pure-spring-water.

The pure-spring-water turned cloudy. The salesman announced the reaction proved the man was suffering from diseased lungs.

He then poured some of the liquid from his miraculous elixir into the glass containing the cloudy spring-water. It cleared instantly demonstrating the potent effect of the nostrum he was selling in eliminating the "disease".

Wot the?

Send your thoughts to the editor

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Best answers will be published in the next newsletter.

