



Proceedings of the 8th LRI Members Workshop

15 – 16 November 2006

Amigo Hotel, Brussels



Executive Summary

The 8th annual LRI workshop that took place on 15 and 16 November in Brussels fulfilled two objectives: to launch and discuss the immediate strategy and themes for the 3rd phase of the Cefic-LRI programme and to undertake a foresight workshop on the subject of epigenetic and transgenerational effects that is an emerging science of potential concern for the chemical industry and society in general.

During first day plenary sessions LRI Phase III strategy was discussed and endorsed as were the three focus areas for action in 2007: Human biomonitoring, Endocrine, and PBT. The second day saw a new workshop structure to explore current knowledge on epigenetics and to consider the possibilities for a LRI/ industry response.

Delegates were united in their view that epigenetics was an important emerging science that could have a significant impact on the industry and on societal perspectives of environmental health. LRI should engage in exploratory research to better understand the mechanisms involved. There was a clear consensus that any research activity should be closely integrated with communication activity on this subject from the start.

Ideas for components of a LRI programme in epigenetics were suggested. Liaison along the supply chain was seen as important and a communications strategy was required soon as it was possible that the topic would fall into the public domain without the scientific understanding being complete. The industry should engage positively and not be defensive on this issue as it is much wider than only chemicals with a potential for all and any environmental stressor able to be demonstrated as producing epigenetic effects.

The workshop format used in the second day was generally perceived as a success and was seen as a good model for early discussions on emerging sciences programme development in LRI.

LRI Phase III

The workshop officially launched the third phase of the LRI programme.

In his welcoming speech to over 100 delegates attending the workshop, **Cefic Director General Alain Perroy** reaffirmed



the industry's commitment to LRI as it marks a new approach that is forward looking and encompasses a

revised strategy tailored to a new system in the post-REACH era. He said the "risk assessment and other tools developed [by LRI] for REACH implementation were extremely valuable to the industry" and described the new LRI programme as "sustainable" and with sufficient funding to make a further good impact over the next five years. The Cefic-LRI programme needed to support a fast and strong implementation of REACH by the industry but also needed to investigate emerging science and issues.

LRI Planning Group chairman Urban Jacobsson of Exxon Mobil outlined the objectives and strategy of the programme over 2007 - 2011. LRI's objectives remain to maintain science-based and cost-effective approaches to risk assessment, and to make a distinctive industry contribution in areas



where its resources can make a difference. In particular this means seeking practical

solutions in a timely fashion, engaging with other stakeholders, building capacity in the industry and being seen to address issues of concern in a proactive manner.

Increasing the value of LRI is important. LRI research results must increase the impact in terms of its contribution to the science and this can be achieved by a tighter focus on a smaller number of larger projects. The use and application of the results needs to be sharpened through a stronger link to current and future industry issues. The excellent work that LRI does must be recognised more widely – LRI needs to be truly recognised as 'doing the right thing'. This can be achieved by building up the LRI science foresight activities with increased external academic peer input – e.g. the epigenetics workshop. The LRI process must also be simplified to increase transparency and make it easier for researchers to engage with LRI. The concept of annual calls for larger projects will help here.

Three general themes for Phase III:

- **emerging concerns of importance to industry** (impact on children, focus on smaller sub-populations, delayed generational effects, individual susceptibility)
- **health impact of real complexity environments** (body burden, bio-monitoring, mixtures, and multi-causal pathways)
- and practical product stewardship concerns that can be grouped under **'Intelligent Testing'** (Animal alternatives, effective authorisation).

Each year the LRI programme will focus on a small number of research calls in the three thematic areas. Typically this will involve funding for three core major projects but smaller applied and foresight activities will also be undertaken. LRI will work to an

annual cycle around the LRI Autumn Workshop where the main themes for the following year will be announced and discussed. The themes will be selected based on a strategic selection that involved foresight activities and expert external perspectives.

The themes for 2007 are **Biomonitoring**, **Endocrine** and **PBT** with two prominent foresight activities – epigenetics and trans-generational effect and pre-work on a likely significant theme for 2008 on Animal Alternatives. This area has already seen substantial activity in support of the 3Rs approach and in particular building the work of the European Partnership for Alternative Approaches to animal testing (EPAA).

2007 Focus – three priority areas

Chris Money of ExxonMobil described how LRI can continue to help the science of **biomonitoring** in the new programme. Money stated that "Biomonitoring is not new - it has been rediscovered." It has been used

in occupational health for decades but there is a new public health emphasis. He also accused some groups of misusing the concept "to play



on the fear of hazardous chemicals and body burdens" with the public. A global programme on human biomonitoring (HBM) was taking shape through the ICCA-LRI focused on increasing the quality of HBM, better use of HBM and how its use could add value. Three areas of work had been identified: exposure, dose and HBM; computational tools for HBM; and HBM and the design of toxicological tools. Cefic-LRI was and would contribute in all areas, but Money highlighted a challenge to ensure that all HBM studies and their interpretation were conducted in a rigorous manner. This was a task that require a broad consensus on procedure, methodology etc.

Gernot Klotz of Bayer (and incoming executive director Research & Innovation) outlined the continuing efforts on **endocrine disrupting (ED)** chemicals. New topics included female reproductive issues, practical testing strategies for REACH and approaches to low dose and possible long-term cocktail effects. Intelligent testing for reproductive toxicity in the spirit of 3Rs

should be given fast track validation to justify use under REACH. He stated that intelligent testing strategies were important in this area – and for chemicals in general. Klotz emphasised that "Endocrine active substances were not endocrine disrupting substances." Other emerging health issues in this area for 2007 include capacity building on neurodevelopment disorders, wildlife and human health.

The third theme area, **Persistence, Bioaccumulation and Toxicity (PBT)**, was described by **Paul Thomas of Akzo Nobel**. Here there is work to complete modelling suites addressing bio-availability and risk assessment as a contribution to the new Cefic Task force on PBT and in REACH authorisation. The role of QSARs and multimedia modelling would be important. Empirical scientific evidence still lacking in a number of areas including accurate determination of half life, biotransformation and mode of actions. Critical body burden also needs major progress and should be taken into consideration for future LRI research.



To complete the plenary sessions on day one the **2005 LRI award winner Dr. Paul van den Brink** of Wageningen University gave a progress report on his winning project on 'Predicting the response of aquatic invertebrates to chemical stress using species traits and stressor mode of action' The study had good links with **bio-monitoring in terms of ecological risk assessment**. Of

particular note was the clear peer-acknowledged value of the LRI award. As with the previous winner (Dr. Roger Godschalk), van den Brink had been able to attract considerable further funding and prestige. The LRI award has a significant impact on the career path of the winners.

Following a pre-dinner poster session with contributions from over a dozen LRI-funded projects, **Martha Heitzmann of the OECD Environment Directorate** gave the keynote dinner presentation on "**Risk Assessment in a Complex World**". She highlighted differences between a risk assessment approach and the precautionary approach to policy making for risk management, and the growing awareness of policy makers to the potential link between environmental pollution, chronic illness and child health issues. Setting the right level of balance between the two approaches was critical and required timely, high quality science input – LRI had a clear role in providing such input.

Epigenetics issue

On the second day of the LRI workshop, scientists from industry, academia and the EU Commission discussed the emerging science of epigenetics. Four parallel sessions laid the groundwork for the development of a future integrated science and communication programme in this challenging area that links environmental factors with transgenerational effects.

Dr. Tim Gant, Chair of the LRI ESAP, gave an initial overview of the science. He offered the following definition of transgenerational epigenetics: "the inheritance of genomic instability resulting from an inherited DNA modification not involving mutation" - the key was that this

could lead to a change in gene expression or a mutation in subsequent generations.

Prof Jay Goodman of Michigan State University, a leading expert in the area, then gave a presentation on “Epigenetics and Transgenerational Effects: Implications for safety assessment of chemicals”. There are two possible mechanisms for inducing



epigenetic effects: alteration of the degree of methylation of DNA; and changes in the acetylating of the complex histone proteins around which DNA is wrapped. Both

Gant and Goodman focused on experimental evidence relating to methylation effects.

Prof. Goodman presented a number of impressive experimental examples of epigenetic effects induced in the laboratory. There was a pressing need to better understand these models and he saw the area as still an area for exploratory research but including initial concepts of what basic toxicity screening experiments might look like. During discussion Prof Goodman pointed out that although the science was young it was moving closer to the public’s attention.

Both speakers concluded that epigenetic effects do happen. Many chemicals have the potential to modify DNA methylation and new techniques now give the opportunity to start to understand how epigenetics and chemical modification of DNA happens and the potential impact on human health including cancer. Epigenetic effects may also be induced by a wide variety of environmental stressors.

LRI epigenetic research?

The four parallel syndicate sessions then looked at the issue from the point of view of **product stewardship, science and regulatory policies, the toxicological sciences, and advocacy and communications**. All four sessions were asked to try to answer three questions:

- What is the importance and relevance of this science?
- What are the likely impacts on the chemical industry?
- What (if anything) should LRI do?

Reports from all four syndicate sessions showed a degree of commonality in seeing a need to formulate an exploratory LRI programme in the area to support research on our understanding of epigenetics, the potential for positive aspects and the need to ensure full integration of science and communication activity in any proposed programme.

It was clear that “doing nothing” was not an option.



Investment in research is required with early engagement through joint stakeholder workshops.

Options for investigation included:

- dose-response and thresholds;
- the contribution of chemicals compared with other stressors (diet, smoking etc.);
- systematic literature study on epigenetic effects;
- development of methods (including in-vitro methods) for measuring changes in DNA methylation status;
- identification of appropriate biomarkers;
- can changes accumulate over successive generations?
- can conventional toxicological studies enable identification of heritable epigenetic changes?
- do benign exposures result in epigenetic changes?

There was a view that the industry should work closely with partners in supply chain. It was important to engage in the issues and take a collaborative approach with key stakeholders and international organizations such as WHO, ILO and key NGOs. This is not only a chemical issue.



Transgenerational effects are potentially an extremely important concern to society in general.

There is a need to review what is already known in detail, monitor the science (a

potential role for ECETOC here?) and get to understand the normal variation/background/baseline/role - for example we do not know what a 'normal methylation' state is.

What is the role for epidemiology? As populations are getting older, often multiple generations are available. Gene profiles can be compared.

The potential danger for the industry is a possibility of a reversion to the precautionary principle if experimental data indicate heritable effects and/ or additional safety factors could be imposed on chemical exposures. It could impact on the REACH process through CMR, equivalent concern and authorisation. It could also be a huge issue from an environmental perspective.

There was a clear need to develop/modify, validate test methods and take regulatory policy into consideration. At present no test methods exist so there is a possibility that studies could lead to banning or attempts to ban products. However it was agreed that the industry must not go defensive on this topic. Epigenetics could provide a potential tool/technology to monitor exposure and/or changes in life style. It could be a useful tool in occupational settings.

Communication is seen as very important and a great deal of thought is needed to get these complex issues across to the general public. A general consensus emerged on the need for funding of the issue.

Epigenetics is a real challenge for the industry and it could come into the public domain without the science being established. Establishing a sound basis for our understanding of epigenetics could yield positive applications in terms of susceptibility and the tailoring of pharmaceuticals to individual needs.