**Sixth LRI Member Workshop**
**Le Meridien Hotel, Brussels**
**November 17 – 18, 2004**

# FIVE YEARS OF ADVANCES IN HEALTH AND ENVIRONMENTAL SCIENCES

This year's member workshop attracted a record number of participants representing industry, the scientific community, government organizations and NGOs. The workshop was opened by Mr Alain Perroy, Director General of Cefic. His welcome was followed by an introduction to the workshop by Prof. Geof Randall, Chair of the ECETOC Scientific Committee, and an overview of LRI's scientific achievements by ESAP member Prof. Bo Jansson. Mr Urban Jacobsson, Chair of the LRI planning group, gave an overview of the LRI programme before opening the floor to the guests speakers.

## Managing health and environment issues through science

High on the agenda was the topic of children's health, which has been central to recent political discussions and the focus of targeted scrutiny by society and industry. Mr Colin Humphris, Executive Director of the Cefic's Research and Science Programme, introduced the issue and the keynote speaker, Dr Roberto Bertolini, Director, WHO Division of Technical Support on Health Determinants. Bertolini gave an overview of WHO's Environmental Burden of Disease study which highlights the principal environmental causes of disease and death amongst children in Europe.
Though the main causes are reported to be injury, poor sanitation, lead and air pollution, Bertolini highlighted some specific knowledge gaps and encouraged the development of more research into areas such as chemical testing, epidemiological research, and biomonitoring.

Bertolini then reviewed the decisions taken at the Ministerial Conference in Budapest last June, where health and environment ministers of 35 states adopted the Conference Declaration and the Children's Environmental Health Action Plan for Europe (CEHAPE). These, he said, provided key tools for policy making and guidance in shaping the direction of environment and health processes in Europe for the future. One of the four regional priority goals set by the participants was to "reduce the risk of disease and disability arising from exposure to hazardous chemicals (such as heavy metals), physical agents (such as excessive noise) and biological agents".

Bertolini also highlighted the way forward in the implementation of the Action Plan, describing the role for the European Environment and Health Committee (EEHC) and the European Union's Environment and Health Action Plan for 2004-2010, as the EU's contribution. He closed by describing the future goals for WHO in health and environment, which include comprehensive monitoring of exposure and health effects, better understanding of the links between environment and health, guidelines for risk

management and communication, including the use of the Precautionary Principle, and capacity building amongst health care professionals. “The chemical industry is a partner, not an enemy,” he concluded. “We need to establish a dialogue to attain these goals together.”

Dr. Awni Sarrif introduced the next session by reiterating the LRI vision under which it will operate over the next five years: managing health and environment issues through science.

On the topic of children’s health, Dr David Owen of Shell Chemicals and a member of the ECETOC Task Force on Children’s Health gave a snapshot of a soon-to-be-published ECETOC state-of-the-science review of trends in children’s health and the role of the products of the chemical industry.

On child health trends, the draft report describes an observed increase in asthma. Childhood leukaemia appears to be rising but is still at a very low incidence. However, no trend has been established for neurodevelopmental and reproductive disorders.

According to the report, allergens responsible for respiratory and other allergies are almost invariably proteins, not environmental chemicals. On the other hand, some evidence suggests a role for volatile organic chemicals in aggravating asthma symptoms by irritating the airways.

Though exposure to lead, mercury and PCBs is linked with neurodevelopmental disorders, exposure to environmental levels of these chemicals, except for lead, is not proven to have a significant effect. The main causes of disorders such as autism and Attention Deficit and Hyperactive Disorder (ADHD) are found to be genetic and socio-economic.

Cryptorchidism and hypospadias, male reproductive disorders believed to be linked to parental exposures to hormone modulating chemicals, are found to be related to a variety of non-environmental factors.

Another issue discussed at the workshop was Risk Assessment, which is being increasingly scrutinized in the current chemical management setting. The key elements to a sound chemical management system, Dr. Tom Feijtel of Procter and Gamble explained, are a risk-based approach to the prioritisation of chemicals, tiered risk assessment framework to assess hazard and exposure concurrently, a decision-making system that considers risks, benefits and costs, as well as timely sharing of meaningful and relevant information.

Scientifically, this means developing more intelligent risk assessment methods, including computer-based modelling, collating exposure and effect data, and assessing environmental conditions.

Biomonitoring is another issue of current significance, and Mr. Chris Money of Exxonmobil described the scientific role of biomonitoring data in the risk assessment process. He also described a pilot ICCA LRI global research strategy on biomarkers and biomonitoring, to coordinate workshops and research activities in Europe and the US.

Endocrine Disruption, though it has been receiving less media attention lately, is still an issue that has high significance from a research perspective. Dr Gernot Klotz of Bayer described the intricate political, scientific and social environment in which this issue is evolving. Industry must continue to contribute to the development of harmonised test methods, and the improvement of our understanding of the issue from a scientific standpoint in order maintain its involvement as a stakeholder in the political debate.

Prof. Ian Kimber of Syngenta described the increasing importance of alternative methods for safety assessments that provide animal welfare benefits. He explained that the industry should not focus exclusively on replacement, but embrace all three R's: reduction, refinement and replacement. He also emphasised the need to accomplish this without compromising the integrity and accuracy of existing approaches to safety assessment. Industry requires a coherent approach that provides a structure for the identification of future needs and opportunities and a platform from which industry can interact effectively and proactively with other stakeholders.

The safety of nanotechnology, and specifically nanomaterials, is an issue which is gaining in visibility in the social and political environments. Due to the largely unknown characteristics of nanoparticles, said Dr. David Warheit of DuPont, they could or could not have more toxic properties when inhaled.

It is important to establish clear risk assessment guidelines for these materials. An ECETOC Task Force has been established to clearly define nanomaterials and help evaluate available data on their toxicity.

The day closed with a dinner speech by Dr. Kees van Leeuwen Director of the Institute for Health and Consumer Protection and DG Joint Research Center. He stressed the need for better risk assessment techniques and intelligent risk management by focusing resources on areas of maximum impact.

## HUMAN HEALTH SESSION: Biomonitoring and improved risk assessment

Biomonitoring is seen as one of the priorities in the second phase of the LRI programme, and three of the human health presentations showcased on-going projects using biomonitoring as part of risk assessment methods.

Dr Kevin Chipman presented his project on the hepatocyte proliferation produced by non-genotoxic carcinogens. His work aims to determine novel biomarkers (measurable biological parameters linked to disease) of cancer-causing chemicals. Some "non-genotoxic" (which do not damage DNA) chemical carcinogens induce cancer by

controlling cell growth, proliferation and apoptosis (programmed cell death). The study examines molecular pathways through which these compounds control cell proliferation, which will facilitate risk assessment of non-genotoxic carcinogens to humans by comparing rodent and human cell responses to carcinogens.

Dr Karen Brown discussed a project investigating the biological relevance of low-levels of DNA adducts (compounds which bond to DNA) with genotoxic and carcinogenic properties. Biomonitoring was used to assess risks associated with endogenous and exogenous exposures.
In parallel, Dr Andrew Povey described another project on associations between DNA adducts and gene mutations. The study measured the presence of adducts in human blood, sperm and various tissues and aims to establish links between the incidence of tumours and the presence of DNA adducts as a tool for human risk assessment.

Dr Marc Cronin gave an overview of a workshop sponsored by LRI to help determine appropriate methods of determining dermal permeation of chemicals to meet REACH objectives. The meeting provided recommendations on the use of QSARs, the definition of a standardized protocol as well as recommendations to meet REACH requirements while limiting the use of animal testing.

In the endocrine field, Dr Hofmann outlined the results of the validation of the enhanced toxicity test OECD TG 407 for the detection of endocrine active chemicals. The test can detect substances which have specific hormonally-induced health effects. The reviewers went on to determine the potential hormone-disrupting properties of specific chemicals based on this test. The reviewers conclude that the test is appropriate to determine the potential hormone-disrupting properties of a chemical for risk assessment.

## ENVIRONMENT SESSION: Predictability across species

Predictability in risk assessment was a general theme in the environment session of the LRI workshop. One long-term project presented by Drs. Budzinski, Tarazona and Thompson aims to develop a model to assess the potential bioaccumulation of substances throughout the food chain taking into account different exposure routes. The model, which currently only applies to substances with very well known properties such as PCBs, should be completed by including broader physico-chemical properties of chemicals. Such a model would enable risk-assessment to take into account potential long-term doses of persistent chemicals at different levels of the food chain.

In a similar vein, a recently completed project, which was presented by Prof Michael MacLachlan, evaluated the applicability of models predicting the fate and transport of persistent organic chemicals. As part of its review, the project team made recommendations on how to improve the existing models, particularly by including

predictions of bioaccumulation in the food chain up to humans. It also stressed the importance of including environmental variability in prediction models.

Another on-going project led by Dr. Roland Nagel comparing soil and sediment toxicity data and test methods has been to explore the possibility to extrapolate ecotoxicity information from aquatic organisms, which is widely available, to sediment and terrestrial organisms, which is more limited. So far, however, lack of data and poor correlation between the toxicity levels of aquatic and soil organisms have made this extrapolation difficult at high concentrations. With additional data such a method would potentially limit the amount of testing required for risk assessment.

A new project called MarSens, initiated in the second phase of the LRI programme, is trying to predict the sensitivity of marine species based on similar freshwater species sensitivity. Carolin Peters discussed the fact that more data is available about freshwater species, and this statistical method could help provide important ecotoxicity data for certain substances. According to the work done so far, there is greater diversity in marine over freshwater environments, which means some exclusively marine organisms need special attention in ecological risk assessment.

So far, statistical analysis showed similar sensitivity for various saltwater and freshwater species to the chemicals tested, but lack of data for marine organisms limits the reliability of the findings. The research team will therefore make recommendations for testing methods and regulation requirements for marine risk assessment.

Aquatic toxicity biomonitoring data can be useful in the development of improved environmental risk assessment and exposure models. To help compile such data LRI sponsored the development of MonitoringBase, a database of European biomonitoring study results for a number of chemicals in water, sediment and living organisms. Such data can be used for further research and risk assessment, limiting the need for additional testing. The database covers all the Water Framework Directive priority list of chemicals except metals and pesticides.

## POSTER SESSION: risk assessment tools

**Respiratory toxicity (J ARTS)**
The three projects aim to provide guidance and tools for risk management procedures on respiratory hypersensitivity-potential of chemicals. The first one examined the role of irritant-induced inflammation in the elicitation of respiratory allergy. The second focused on concentration-response relationships during respiratory allergy elicitation, which would enable the assessment of safe human exposure levels. The third aims at establishing impact of route and intensity of exposure during sensitization.

**ExpoFacts (V TENHOLA)**
ExpoFacts is a tool for environmental exposure analysis and risk assessment, and can be used as a data source for European statistics. The Source book is available on-line and has three parts: a database, a reference guide and a document library. It is a compilation of European exposure factor data from over 100 national and international sources. Available data are demographic, socio-economic, and life-style.

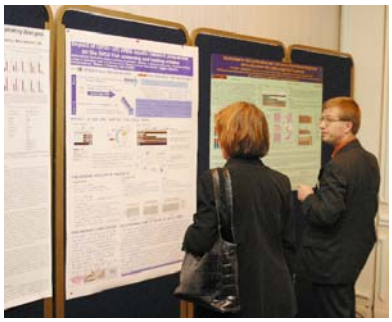
**Development of a database for SAR in repeated dose toxicity (A BITSCH)**
The database was developed to investigate the relationship between chemical functional groups/categories and target organs in repeated dose studies. Each chemical is presented via three core data sets in the database: structural features and physicochemical data; data on study design; study results and effects in target organs with corresponding LOAELs.

**Variability and uncertainty in chemical exposures for regulatory risk assessments (A SOUTAR)**
This project aims to help better define and characterize the risk to chemical exposure, while improving the process of exposure assessment by improving exposure estimates The researchers used and further developed the deterministic model developed by Cherrie et al.. Exposure measurements were placed in a separate database, and combined with the estimated exposure distribution from the modeling to provide updated estimates and to derive reasonable worst case values.

**Gene expression profiling of skin carcinogenesis in mice (K RIDD)**
The studies identified profiles of gene expression associated with tumourigenesis and hyperplasia. Those profiles may be useful in predicting the ability of a compound to promote tumourigenesis, and in establishing more refined estimates in risk evaluation of dermal-active chemicals in humans.

**The likely role of steroidal oestrogens in causing widespread endocrine disruption in wild fish (S JOBLING)**

The hypothesis that estrogenic chemicals in effluents from sewage play a major role in causing sexual disruption in wild fish is supported by growing evidence. Steroid estrogens are the most significant estrogenic compounds in most sewage effluents, but the role of other xenobiotic endocrine disrupters with estrogenic properties – such as 4-t-nonylphenol – has not been comprehensively assessed.



Their concentrations in effluents are relatively low, but when replicated in laboratory experiments, they are high enough to induce vitellogenin synthesis and intersex in some fish species. And since laboratory studies have shown that steroidal estrogens are additive in their effect, it is possible that even where the water concentration of one of these estrogens is below the lowest observable effect concentration, the combined mixture of steroid estrogens present could still cause an effect.

**Biomagnification and critical body burdens (J TARAZONA)**

This poster was intended to promote debate and discussion over the current and future selection of chemicals to be tested and/or modeled for the work being done on Persistence. Ideally the chemicals should be among those not usually studied, with no or low kinetic information and a well-known structure. The project covers 4 main issues requiring testing/modeling of substances:

- Biomagnification – marine organisms testing
- Biomagnification – marine organisms modeling
- Critical body burden – marine organisms testing
- Critical body burden – terrestrial organisms testing

**Perinatal factors and risk for cryptorchidism and hypospadias (A EKBOM)**

This work examines the likely causes of the two major male urogenital malformations, cryptorchidism and hypospadias. His work shows that though the two conditions only partly share prenatal etiology, both are strongly associated with high maternal body mass index. Increased incidences of obesity in society may therefore explain in part the reported increase in these malformations.

## Future directions and wrap-up

The scientific presentations were followed by a brief overview of the LRI Innovative Science Award, which was introduced last year. Dr. Tim Gant described the selection process and spoke of the four finalists' work.

A member's input session led by Mr. Colin Humphris provided an opportunity for participants to voice their opinion of the programme and health and environmental

research overall. Participants underlined the need for strong communication to close the gap between the programme's mission and concrete projects by presenting a complete picture of the projects' findings. The need to link with sector groups within Cefic and regulatory bodies was stressed, as well as the importance of considering social issues. However, one member objected that letting social issues influence the direction of the programme could lead to certain issues getting undeserved importance and visibility while leaving other questions unanswered. The programme's direction therefore needed to be based on significance. Another participant felt the line between fundamental and applied research was being blurred, and that there needed to be increased focus on applied research.

The final panel session, mediated by Kees Van Leeuwen, included Prof. Tom Burns of University of Uppsala and a member of ESAP, Prof Lynn Frewer of Wageningen University and a member of ESAP, Prof Peter-Heinz Gelbke of BASF, Prof Geoff Randall of ECETOC, Prof Vera Rogiers, of Vlaams University in Brussels and a member of ECOPA, and Dr David Warheit of Dupont.

Lynn Frewer spoke on risk communication. She stressed that risk perception does not align with technical priorities of risk but cannot be ignored. In policy, if people think the truth is being hidden trust is taken away. The industry needs to effectively communicate risk. Values apply to risk assessment in priority setting, and all stakeholders need to be involved in the debate.

Vera Rogiers addressed the policy context of REACH, and cosmetics in the context of animal testing alternatives. In FP6 she has been disappointed with the objective of reducing animal testing, as she feels it was not taken seriously. In the context of cosmetics, it is a categorical requirement with a specific deadline to come up with replacement of all animal testing. However, she says, there is not enough work in the pipeline to meet such an objective. "We already know what will be available in 30 years," she said. She feels there is a lack of coordination under FP6 which will lead to broken promises and a decline in public trust. In FP7, she hopes the priority of alternatives will receive the importance it deserves and that all stakeholders will be involved.

Tom Burns presented his views on new ways of thinking, networking and communicating. The concept of stakeholders who participate in decisions is a new one for the industry, and it needs to consider that NGOs have changed politics. Science in itself is not respected anymore, he felt, it is challenged all the time. The situation is more complex, there are new means of approaching issues, public concepts are now part of a process we need to understand and participate in. The industry needs to think about better two-way, participatory approaches to management.
Peter Gelbke talked of the future challenged to industry. Regulatory policy is the outflow of social concern, he said. If we address it, we cope with the fears of the public. The

challenge ahead with REACH is that we are now responsible for risk assessment. We often waited on third parties but now we are responsible. We therefore need the methodology to encompass exposure assessment and effect assessment, and incorporate new methods. While we still need animal experiments, we are stepping forward in alternatives.

Goeff Randall spoke of the importance of public opinion. He said LRI can do is limited, but it should use its knowledge and focus it on the relevant issues. The good science test used to be peer review, he continued, but now, it is much broader. Community in general and the regulatory community has to be satisfied that it is good science. Before we set out to rebuild trust, we must first determine if it is totally ruptured. If so, there is no point, he argues, just more negative feelings. But he feels it is not totally ruptured in the case of the chemical industry. Some people recognise the value of industry contribution. With a decade-long programme such as LRI, we need to engage with all sectors, even negative ones, to learn to work in complex environments.

David Warheit discussed the importance of risk assessment in nanotechnology and said it could face the same public objection as GMOs if proper information is not communicated about risk.

Kees van Leeuwen thanked the participants and closed by saying that LRI is part of a communications process and has built a huge network of scientists. It needs to translate its findings to policy makers and other industries. LRI is a small programme, he continued, so the focus should be on applied science, to do what is most relevant for the industry. There is an important need to look at future savings in cost, animal testing and time. Between 2009 and 2030 there will not be enough alternative test methods to make an impact. We need to think differently: we have found the easy solutions but have not looked at the complex problems. The issue needs a broader perspective to apply characteristics, QSARs, exposure and other data to create intelligent integrated risk assessment methods. On the risk communications issue, he feels LRI must communicate its results to the public. It should take initiative and be resource oriented. LRI should act responsibly and credibly, it should formulate goals, account for conflicting points of view, provide transparency and dialogue. It could also use a neutral party as mediator. Finally, he said the main challenge for the future of the industry is to cope with policy issues. This is not a short term goal, he said, we must continue to improve the chemical management process.

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