Fifth LRI Members' Workshop

Sheraton Hotel, Brussels
November 19-20

Attendance

A total of eighty-five participants attended this year's LRI member workshop, representing industry, academia, European Institutions and NGOs. Participants were drawn from across Europe, and industry representatives from Japan and the United States also took part in the sessions.

Day 1 - Introduction and status

The workshop was inaugurated by Alain Perroy, Cefic Director General, who congratulated the LRI programme, calling it "an immensely important voluntary programme of the industry to demonstrate our willingness and potential to address issues independently and inventively." He called upon participants to take action upon the results of this research to build consensus and establish recognised methodologies. "The role of science is ever more important in today's political world," said Perroy, who explained that increased focus on issues such as body burdens, children-driven risk evaluation and precaution will add challenges for the industry. He expected that sound science will help focus on the right aspects of uncertainty and set priorities for risk assessment. Perroy also emphasized that Cefic continues to be committed to LRI, seeing it as a crucial global contribution from the industry, and that options to make LRI funding more permanent were being explored.

Perroy was followed by Urban Jacobsson, of ExxonMobil and Chair of LRI's Planning Group, who provided a status of the programme, which is concluding its first five-year cycle. He demonstrated the ability of the LRI programme to be responsive and flexible in facing present-day issues and described its benefits at the scientific, but also the reputation level, for the industry. Maximizing relevance and impact by focusing on specific areas and leveraging research budgets by working cooperatively with other organisations has been one of the main successes of LRI, and will continue to be priorities with increasing demands being placed on the industry.

Programme retrospective review

The programme retrospective review session was chaired by Colin Humphris, Executive Director of the Cefic's Research and Science Programme. Gernot Klotz of Bayer and Chair of the LRI's Endocrine Modulators Steering Group (EMSG) Project Team presented a retrospective review of the research which has been done in the area of endocrine disrupters. He demonstrated that as awareness of the issue grew in the public and regulatory arena, LRI-driven research has provided a medium for the industry to contribute valuable information to the debate, as well as build the expertise needed to support further risk assessment developments. LRI's significant contribution to the development and validation of testing methodologies for the OECD has helped it gain recognition as a valuable partner in establishing effective testing and related policies.

Going forward, Klotz pointed out the disparities between perception and reality when assessing actual exposure to man-made chemicals with suspected endocrine disrupting functions, and called for industry and regulators to continue working together on harmonised approaches using the weight of evidence, and a comprehensive approach examining the role of natural and synthetic hormones as well as other non chemical factors. He predicted that research in the field of endocrine disruption will continue to be critical in the next few years.

Tom Feijtel of Procter and Gamble and Chair of the LRI Environmental Project Group then provided an overview of LRI research in the environmental arena. Mr Feijtel recalled the objectives of the project, which concentrates on the improvement and validation of fate and distribution models; marine risk assessment; and PBTs and long-term risk to Ecosystems. In each one of these areas, LRI results has delivered some compelling results, with the development of a series of environmental models, completed work on comparisons between Marine and Fresh Water toxicity, and a study allowing to define Persistency and help establish refined test methods measuring the fate of chemicals in marine and terrestrial environments. Feijtel also described the increasing recognition gained by the programme amongst regulatory and scientific communities for its contribution in areas such as Quantitative Structure-Activity Relationships (QSARs), toxicogenomics, persistency and environmental monitoring. He then provided a glimpse of challenges to come with topics such as animal alternatives, -omics, REACH and the Water Framework Directive driving future research needs.

The Chair of the Human Health Project Group, Chris Money of ExxonMobil, then presented the human health research accomplishments of LRI. He pointed out that some of the recommended areas for research identified at the beginning of the programme as having less impact at the time have gained significant importance, and stressed the fact that LRI should be as forward-looking in the long term as it has been in the short to medium term. He did acknowledge that early recognition of the importance of certain issues such as consumer exposure and repeat dose toxicity have allowed the industry to be ahead of the curve in research in these areas. He also mentioned two noteworthy LRI projects which have delivered significant results allowing for early identification of carcinogens and human health risk assessment and the identification of chemicals causing allergic sensitisation. Money stressed the importance of continuing the work initiated so far and establish further cooperative relationships with other organisations to gain additional leverage for the research.

External Science Advisory Panel Chair Peter Calow provided a positive review of the programme, while deploring a trend where policy and regulations are increasingly based on less relevant science. “Is science under threat,” he asked? As legislation is increasingly based on less and less relevant data, LRI will need to demonstrate that improved understanding based on hard evidence is the best base for policy development. He also stressed that in light of the need to address an increasing number of issues, LRI will need to ensure the programme is increasingly cost effective. “LRI science is sound, said Calow, and I’m impressed with the breadth of its activities given its limited resources. I hope it continues in this way.” Communication, he concluded, is key to the programme’s long-term success.

David Owen, Chair of the Children’s Health and Environment Issue Management Team, discussed the challenges faced by the industry in a political environment where questions relating to children and sensitive subpopulations, and the uncertainties related to them, are increasingly in focus. In addressing the key questions raised on the potential sensitivity of children, Cefic has setup an Issue Management Team which looks at three aspects: the

science, communication and advocacy. Owen then described some of the work the IMT has accomplished so far, including sponsorship of a workshop dedicated to children's exposure, working together with ECETOC on the establishment of a Task Force; a State of the Science review to be published in early 2004; and addressing immediate political agenda such as SCALE. He stressed the fact that children's health is a global issue which will gain visibility and will require commitment from the industry.

REACH and (Q)SARs

This was followed by a presentation by Jack de Bruijn, of the Environmental Chemicals Bureau, who gave an overview of research in the context of REACH, and the new sciences to be integrated into the risk assessment process. He explained the role of the Chemical Safety Report and the use for exposure scenarios, which will detail how chemicals are processed and used as well as their characteristics to enhance risk assessment. In the new REACH risk assessment paradigm, de Bruijn says, producers can choose to respond in different ways to the outcome of a risk assessment at each stage, by increasing classification, performing more research for characterisation, or increasing risk management measures. De Bruijn then described how QSARs can become an important tool under REACH, allowing for the reduction of animal testing and rapid decision-making, but they will require the development of guidelines for validation and sharing of data. Finally, de Bruijn explained how the precautionary principle will be applied as a method of risk management, in cases where risk cannot be determined with sufficient certainty. This will specifically apply, he says, to chemicals such as Carcinogenic, Mutagenic and Reproductive (CMR), Persistent, Bioaccumulative and Toxic (PBT) and Endocrine Disrupting substances.

His speech was followed by a presentation by Watze de Wolf, Chairman of the LRI QSAR Monitoring Team, who described the benefits and shortfalls of QSARs for Risk Assessment, explained there are some limitations in the use of QSARs, but they can be precious tools in specific situations. The scope for QSAR use, says de Wolf, includes risk-based prioritization, risk assessment to establish need for further testing and some classification. Limitations include the variability and shortage of available data, over-simplification when used with complex endpoints, and lack of support tools to help the users. He emphasised the fact that complementary testing will be necessary for human health risk assessments, and called for the implementation of criteria and harmonised processes and validation methods, as well as training, for the use of QSARs. De Wolf then gave an overview of the work done by the industry, through LRI, to establish consensus on the use of QSARs, together with the OECD and other stakeholders, as well as research on the implementation of QSARs to a broader range of products.

LRI Innovative Science Award and conclusions

Peter Calow then presented the new LRI Innovative Science Award, which will be presented in conjunction with Eurotox in 2004. The €100k award will given to an early career Europe-based scientist who proposes novel interdisciplinary research in the field of toxicology. The award aims to support creative new research in the field of toxicology. Calow gave a glimpse of the publicity being done to promote the award, and described the timeline for the selection process.

Urban Jacobsson then closed the day's sessions by summarising the new issues being faced by the industry, which are "taking us into un-chartered territories," he said. New regulations, new research methods which should help fill the 'toolbox' needed to respond to these regulations, as well as the prioritisation of Risk and use of precaution will all present great challenges in the years to come. "The use of less relevant evidence [in regulatory decisions] means evidence needs to be more relevant," stressed Jacobsson, who concluded by re-emphasizing the relevance of LRI in the context of the regulatory framework.

The day was followed by a cocktail and dinner hosted by Cefic Research and Science Board Chair Mike Buzzacott of BP Chemicals, where David Gee of the European Environment Bureau gave insights on his perceptions of the industry's research programme, raising the question of whether the industry was seriously trying to address issues or simply trying to present a positive image.

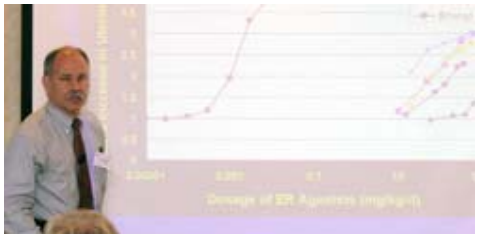
Day 2 – Scientific Sessions

Participants split into two parallel sessions for day two of the seminar. The Human Health session was mediated by Tim Gant, of the Medical Research Council of Leicester University and an ESAP panellist, while the Environment session was chaired by Peter Douben of Unilever, and a member of the LRI Planning Group.

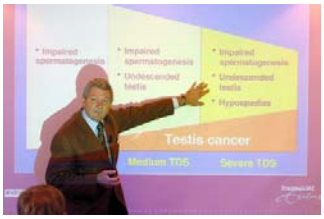
Human Health Session

The first presentation in the human health session was in the area of workplace exposure. Derk Brouwer, of TNO University, presented a project on skin protection strategies. The study aimed to evaluate the performance of personal protective equipment for dermal exposure to reduce uncertainty in estimates of skin protection. The research involved developing dermal exposure models and scenarios, and evaluating current techniques for calculating dermal exposure.

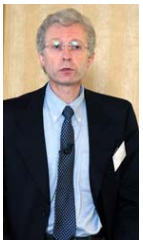
Next, Hak Kan Lai of Imperial College presented work on the EXPOLIS study, which aims to provide a database of human exposure patterns and models for health risk assessment in Europe. The study combines a representative sample of urban populations throughout Europe and takes factors such as activity, home exposure, and meteorological data into consideration. The study found that time spent indoors is an important determinant of exposure patterns, and that modelling home indoor levels of pollutants is essential in health risk assessment.



William Owens of Procter and Gamble, formerly head of the OECD team on endocrine disruption testing and assessment, then provided an overview of the work LRI has done to contribute to the screening and validation of three endocrine testing assays. He showed the efficiency of the assays in measuring endocrine-related endpoints, and praised LRI for its valuable contribution to the validation of these assays to enhance the reliability of endocrine disruption detection.



Researchers Rob Weber and Frank Pierik, of Erasmus University, presented their work on an epidemiological research on reproductive development. The study, which evaluates potential links between exposure to endocrine disrupters and an increased incidence in male reproductive system abnormalities, concluded that no relation could be made between maternal exposure to suspected endocrine disrupters and these anomalies, while other factors such as smoking, ethnicity, general health, maternal age and paternal job function were linked to the conditions.



The next study on the relevance of rodent carcinogenesis studies to human health was presented by William Watson of Syngenta. The study aimed to establish safe and relevant exposure limits for carcinogenic chemicals based on rodent cancer studies and examining molecular mechanisms involved in carcinogenesis. The study showed significant differences both in vitro and in vivo in response to carcinogens, and therefore concluded that mechanistic studies should be included in human risk assessment and setting safe exposure levels.

The final presentation in the human health session was made by Harry van Steeg, of RIVM, who talked about altered gene expression in mice exposed to carcinogenic compounds. The study aims to help identify the carcinogenic risk of substances at an early stage and limit the need for animal testing by using transgenic mice sensitive to carcinogens. The study showed that the use of transgenic mice was reliable for the detection of human carcinogens, and that the combination of using transgenic mice with micro array technology would provide a promising tool in cancer risk assessment while helping reduce the need for animal testing.

Environmental Session

The first presentation of the Environmental session was by Jochen Rominger, of Technidata. He presented the software model system GREATER-II, a geography-referenced exposure assessment tool that allows to predict chemical fate and exposure in surface waters. GREATER combines the use of models with GIS information, as well as easy-to-use graphical interfaces and a web-based application. In a demo, Rominger showed how substance concentrations are calculated based on a set of modifiable parameters. Rominger also discussed the European Environmental Agency's collaboration on GREATER, and explained the tool may be integrated in regulatory risk assessment tool sets.

"Where GREATER ends, GEMCO begins," introduced the next presenter, Johan Boon of Delft Hydraulics who described the GEMCO model for estuary contaminants. The generic model helps understand and forecast the fate, distribution and impact of contaminants in estuaries. This tool provides a means to determine sediment and water concentrations in an estuary as well as the transport of contaminants through the food web, allowing for better risk assessment of chemical production and discharge.

TERRACE was the next model presented during the session by Sue White, of Cranfield University. This model evaluates terrestrial runoff of chemicals using variables such as changing land surface characteristics contaminant input and is spatially distributed. Contrary to existing models, TERRACE evaluates substance run-off, therefore providing evaluations of diffuse pollution and watershed contamination, a feature essential within the Water Framework Directive.

Another model, for atmospheric deposition and transport, called ADEPT was presented by Michiel Roemer of TNO. This model differs from existing one by integrating higher degrees of spatial and temporal information for more realistic environmental risk assessments. Based on emissions and chemical properties entered into a software interface, the model can generate a map of concentrations and deposition loads over Europe.

David Brooke, of Building Research Establishment, presented a project which aims to improve data sources for use in release estimation. Based on the data collected from various sources, the team created flow charts designed to establish at which level in production and application a chemical may be released in the environment. Based on this, Emission Scenario Documents are created to help refine risk assessment for the substance. This research was done in collaboration with the OECD and is now going through final approval.

Tom Aldenberg of RIVM then talked about the development of tools for probabilistic uncertainty analysis in environmental risk assessment. The project aimed to review current uncertainty analysis methods for ecological risk assessment and address research gaps in calculating methods. As part of the project, researchers will give a short course on methods in probabilistic ecological risk assessment in the US and Europe. A probabilistic analysis software tool was also developed which graphically displays risk assessment results.

A description of LRI's work with the OECD on Endocrine Fish Screens and Assays was then given by Patrick Suteau of Bayer Crop Science. He provided details of each project, aimed at developing cost effective test methods for endocrine disrupters in fish. These screens and assays are being validated by the OECD.

Peter Douben then gave a brief overview of the work being done on Persistency at LRI. The research aims to looks at how regulatory risk assessment deals with PBTs and recommend exposure risk-based approaches for handling PBTs in the regulatory framework. He explained that current methods for determining persistency are inadequate and specific to individual components. This work by LRI is getting support and cooperation from industry and governmental organisations.

Jason Snape of Astra Zeneca then presented a study on assessing chemicals' persistency which helps define persistence and the factors that affect the persistence of chemicals. It also provides relevant information to help develop better ways of measuring the fate of chemicals in the environment. Models, screens and test

methods can be based on this information, which has drawn a lot of interest and support from government and environment regulators.

Future Drivers Session

The first presentation in the afternoon session was given by Alberto Mantovani, of the Italian National Health Institute. Mantovani explained the raison d'être of the new European Environment and Health Strategy (SCALE), and detailed the work being done in the area of endocrine disruption. This work aims to evaluate available information and gaps in knowledge in endocrine disruption, as well as establish priorities of action in the area. The outcome should be a working model for integrating different database to implement a European monitoring system.

Jan van der Valk of the Netherlands Centre on Alternative Animal Use (NCA) then gave a presentation on research needs for animal alternatives. He gave a sense of the current motives and challenges in implementing alternative techniques, provided an overview of existing validated tests for risk assessment, and presented some of the emerging approaches for alternative testing. Van der Valk also proposed a system whereby test data would be shared in a central repository, reducing the need for duplication of testing, and tiered approaches to testing would be used. Prioritisation and more investment from regulatory and industry are required, he said, in order to move this forward. "Less animals make better science and better science makes better risk assessments," he concluded.

Following his presentation, Ian Kimber gave an overview of LRI's new Alternative Approaches to safety Assessment Strategy group, which was formed to review what is currently being done within the industry on implementing alternatives, and identify gaps where additional research would be required. The group is working with ECETOC to address these gaps and aims to provide a more coherent way for the Chemical Industry to implement alternatives and interact with other stakeholders on the issue.

Lynn Frewer, of the University of Wageningen and an ESAP panellist, then provided input from ESAP on LRI's communication and credibility needs. She highlighted the increased needs for transparency and public trust in today's societal context, and provided some tips on developing and maintaining credibility, including the need to work with other institutions and stakeholders. She then spent some time describing the process of risk perception and communication, and recommended broader dissemination of LRI's research results, as well as the possibility to institute a 'Science Communication Award' as an incentive for researchers to communicate their results beyond the scientific community. As a means of furthering LRI involvement in the area of risk communication, she also presented the concept of a multi-stakeholder workshop to identify and refine potential research topics, which would then feed into the LRI process.

Panel Discussion

A panel discussion chaired by Peter Calow was then organised on the various topics raised over the two-day workshop. On the topic of communications, Matti Jantunen of KTL and an ESAP member talked about the fact that the scientific community is seen as biased, and the issues resulting from perceived – or actual – 'hidden agenda' of communicators. Lynn Frewer responsded that she felt the concept of hidden agenda was addressed with transparency. Colin Humprhis underlined that programmes such as Cefic's Trust and Reputation were trying to address this, but that it was not only a scientific issue but also an emotional one. Tom Feijtel reinforced this point, saying that consumers and NGOs did

not speak the same language as scientists, and therefore there was no understanding between parties. “How do you communicate fact versus emotion,” he asked? Gernot Klotz underlined the issue was not just in risk communication, but in overall science advocacy, and in specifically addressing consumer issues. Chris Money stated that industry has a role to play in demonstrating the role of science in addressing issues. “This should be part of our responsibilities under Responsible Care,” he said. Coordinated efforts across the industry would provide a stronger response. Lynn Frewer then said that the way issues are presented by the scientific community is not understood by the public, and that the perspective of the target audience should be used when addressing issues. Gerhard Winneke of the Medical Institute of Environmental Hygiene and an ESAP panellist felt science does not speak with one voice, as results and interpretation differ between scientists, which makes it difficult to explain to the public. “We need to explain why science does not necessarily cancel-out each other,” he said.

On the topic of Sensitive Groups, Matti Jantunen felt ‘sensitive subpopulations’ needs to be better defined to establish whether or not these groups should be treated differently from the rest of society. Alberto Mantovani talked about the interplay between environmental factors, lifestyle and socio-economic factors which affect exposure and risk awareness. He felt a more holistic point of view to cover all areas should be considered. Gernot Klotz reflected that society must see that some sensitivities need to be addressed individually. If controls are too lax, he says, then a significant minority of the population is at risk, but if they are too tight, a majority of the population lose the associated benefits. Tim Gant of the University of Leicester and a member of ESAP, expressed the opinion that sensitivity can be based on genetic vs immunity or other factors. Gerhard Winneke pointed out that results of research on differences in genes have been disappointing so far. Only in some instances are genetic sensitivities proven. Tim Gant replied that we may not be able to define these differences, but the future may show better results on multiple-gene effects. Peter Calow asked whether this required a refinement of risk assessment methods, to which Tim Gant replied that the influence of genetic vulnerability is well defined in the pharmaceutical sector. This is addressed by using less variable test generations, and therefore the same could be done with chemicals.

On the Precautionary Principle, Joseph Vos of RIVM expressed the opinion that while he agreed with the fact that in PBTs risk was unacceptable, this was not the case for endocrine disrupters. He stressed that endocrine disruption is a mechanism, and that substances should not be labelled according to their endocrine modulating properties but based on specific health end-points such as reproductive toxicity. Peter Douben talked about defining acceptable risk by looking at exposure and exposure potential. He felt that if exposure potential can be lowered, then risk can be lowered. He also stressed that acceptability is a social, not scientific value. Through better science, though, we can understand certain aspects of chemicals, providing this is done in a certain containment. Colin Humphris pointed out that uncertainty sometimes is based on lack of knowledge, controversy or complexity, and asked what the industry was doing to address lack of knowledge. Carol Henry of ACC referred to the Persistency work presented earlier that day by Jason Snape, saying it addressed some of the uncertainties linked to PBTs and could be used to help screen and prioritise substances. She felt work being done in the environmental area could help deal tread through the complexities of the human health area. Louis Bloemen of Dow Europe talked about the strengths and weaknesses of epidemiology and the difficulties in reproducing

results when conflicts occur, which are a barrier to reducing uncertainty. He felt caution should be used in communicating results until credibility could be built up with further testing. In response, Gernot Klotz felt that the more research is done, the more diffuse it gets, resulting in perceptions of increased uncertainties. Criteria for communication should be developed, he said. Non-findings should also be published, he said, which would help reduce uncertainty. He expressed disappointment in the fact that epidemiologists do not factor in other aspects, such as public health, into their findings, which translates in misunderstandings and misinterpretations. Tom Feijtel concluded the discussion by reminding the audience that LRI is working on developing ways to work its findings into risk assessments in Europe, and that the research done also deals with uncertainty. He felt science needs to fill knowledge gaps to be able to do proper risk assessment.

Conclusions

The day was closed with a review by Urban Jacobsson of the potential future objectives LRI will be considering in its second cycle of research. Addressing public perceptions and emotions, which drive the legislative and market forces, will become a major driver in future directions, as regulation will be based on less and less relevant evidence. Other drivers include public opinion trends such as linking chemical exposure and broad health trends; increased attention given to occupational and indoor health exposure and a special emphasis on children exposure; the implementation of REACH which will lead to an increased need for testing and data acquisition; and the introduction of new technologies and risk assessment methods needing harmonisation and validation.

Today's LRI research portfolio is relevant to all the identified issues, he said, but there is a need to re-evaluate priorities.
Increased involvement in the development and implementation of new science themes should be explored, including:

- 'intelligent testing strategies' (such as alternatives to animal testing);
- relevance of environmental research (specifically on persistency) to human health;
- impact of man-made vs natural endocrine disrupting substances and mixtures;
- susceptible subpopulations;
- and involvement in monitoring and evaluating emerging sciences (-omics).

He also stressed the need for LRI to increase its impact by integrating science and technical issues with advocacy and communication efforts, and talked about possibilities for future leverage through technology platforms. Finally, he spoke of the efforts to initiate a more transparent global ICCA LRI planning process to ensure that global issues are addressed effectively and efficiently.

"We must be more alert to public issues and bring relevant science to the public debate in a timely fashion," continued Jacobsson. "There is an old saying: You never get a second chance to make a first impression," he concluded. He explained that all the potential new initiatives and objectives would be discussed and prioritized over the next few months by the LRI Planning Group.

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