WORKSHOP OVERVIEW

It is becoming increasingly apparent that the genetic toxicology community should move away from qualitative hazard-based approaches to quantitative risk-based methodologies to facilitate data interpretation in the context of informing human risk. Given that genetic toxicologists employ a number of different in vitro as well as in vivo test systems, it is imperative that approaches for comparing the dose-metrics across the test systems be standardized so that a point of departure (POD) or no-observed-genotoxic-effect-level (NOGEL) derived in one test system can be extrapolated or compared to another and eventually from experimental models to humans.

This workshop is organized by the HESI Genetic Toxicology Technical Committee (GTTC), formerly known as the IVGT. It will bring together experts in the fields of genetic and general toxicology, risk assessment, and computational biology representing industry, academia, and government to address and make recommendations on a path forward on this topic, including the identification of any key data gaps in our knowledge that require further research. While the focus of this workshop is on genetic toxicology studies, the key learnings from this effort will have a much broader impact across various toxicology disciplines.

ORGANIZING COMMITTEE

Dr. Bhaskar Gollapudi, Exponent, USA
Dr. George Johnson, University of Swansea, United Kingdom
Dr. Matthew LeBaron, The Dow Chemical Company, USA
Dr. Anthony Lynch, GlaxoSmithKline, United Kingdom
Dr. Frank Martin, Lancaster University, United Kingdom
Dr. Stefan Pfuhler, Proctor and Gamble, USA
Dr. Veronique Thybaud, Sanofi, France
Dr. Jan van Benthem, Research Institute for Public Health and the Environment (RIVM), Netherlands
Dr. Paul White, Health Canada, Canada

STAFF

Dr. Connie Chen, ILSI Health and Environmental Sciences Institute, USA
Ms. Brianna Farr, ILSI Health and Environmental Sciences Institute, USA
Dr. Jennifer Young Tanir, ILSI Health and Environmental Sciences Institute, USA

Additional support for the workshop provided by the HESI Genetic Toxicology Technical Committee.

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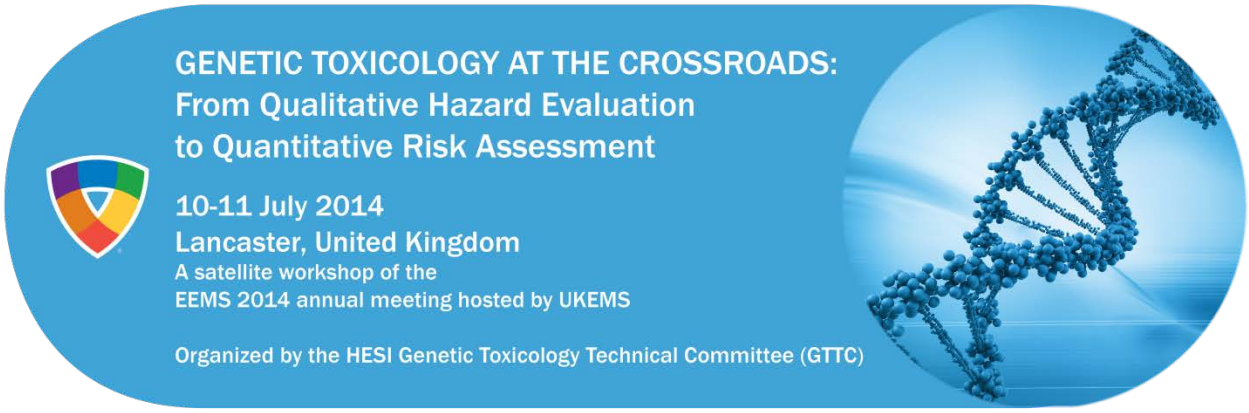


DETAILED AGENDA

Location: Lancaster University, George Fox Centre, Lecture Theatre 1

Thursday 10 July 2014

12:45 pm: Workshop registration open

1:15 pm: Workshop starts

1. *1:15 pm – 1:30 pm*
   Introduction: Towards a New Paradigm in Genetic Toxicology: From Qualitative to Quantitative Approaches – Bhaskar Gollapudi (Exponent, USA)
2. *1:30 pm – 2:15 pm*
   Plenary Lecture I: PK and PD Tools for DNA-Damage Pathways: Modeling Dose Metrics and DNA-Repair Processes – Mel Andersen (The Hamner Institutes, USA)
3. *2:15 pm – 6:15 pm*
   Session I: **Metrics of Quantitative Approach of Genotoxicity**
   Session Chairs: Veronique Thybaud (Sanofi, France) and Bhaskar Gollapudi (Exponent, USA)
   a. *2:15 pm – 2:35 pm*
      IWGT Workgroup Recommendations for Quantitative Assessment of Dose-Response in Genetic Toxicology - George Johnson (Swansea University, UK)
   b. *2:35 pm – 2:55pm*
      A Toolbox to Estimate Point-of-Departure Metrics in Genetic Toxicology – Paul White (Health Canada, Canada)
   c. *2:55 pm – 3:15 pm*
      Biological Processes Driving the Response to Low Doses – George Johnson (Swansea University, UK)
   d. *3:15 pm – 3:35 pm*
      Application of the TT21C Strategy to Safety Assessment for DNA Damaging Compounds Using Quercetin as a Case Study – Rebecca Clewell (The Hamner Institutes, USA)

e. *3:35 pm – 4:00 pm*
   Afternoon tea break
f. *4:00 pm – 4:20 pm*
   Qualitative and Quantitative Approaches on the Threshold of Genotoxic Carcinogens – Shoji Fukushima (Japan Bioassay Research Center, Japan)
g. *4:20 pm – 4:40 pm*
   Benchmark Dose for Genetox and Cancer Endpoints and Correlating between Systems – Wout Slob (RIVM, Netherlands)
h. *4:40 pm – 5:00 pm*
   Update on IGG Work of In Vitro Risk Assessment – Ann Doherty (AstraZeneca, UK)
i. *5:00 pm – 6:15 pm*
   Panel Discussion

   Discussion Questions:

   - Do we have enough scientific rationale and relevant examples that support moving from qualitative to quantitative approach for genetic damage whatever the types of compounds?
   - What are the most appropriate test systems and endpoints?
   - Are the proposed metrics adequate and ready for use?
   - What would be needed to more efficiently move forward?

4. *7:00 pm – 9:00 pm*
   Banquet Dinner *(The Midland Hotel, in Morecambe; transportation will be provided).*

Friday 11 July 2014

8:15 am: Coffee available in Foyer

8:30 am: Workshop continues

1. *8:30 am – 9:15 am*
   Plenary Lecture II: Level of Concern for Genotoxic Carcinogens at Human Relevant Exposure – Alan Boobis (Imperial College London, UK)
2. *9:15 am – 11:25 am*
   Session II: **The Measurement and Estimation of Exposure for Better Extrapolation to Human**
   Session Chair: Anthony Lynch (GlaxoSmithKline, UK)
   a. *9:15 am – 9:40 am*
      Integration of Dosimetry and Exposure into In Vitro High-Throughput Screening – Amin Rostami-Hodjegan (The University of Manchester, UK)

b. *9:40 am – 10:05 am*
Computational Tools and Models to Facilitate In Vitro to In Vivo Exposure Extrapolation – Lessons from the Drug Development World – Oscar Della Pasqua (University College London, UK)

c. *10:05 – 10:30 am*
Reverse PB/PK Dosimetry for Extrapolation of Biomonitoring – George Loizou (Health and Safety Laboratory, UK)

d. *10:30 am – 11:00 am*
Panel Discussion

Discussion Questions:

- What are the key lessons for extrapolating "the dose in vitro" to "in vivo exposure" and how may these be applied in genetic toxicology testing?
- How do limitations of in vitro models impact such extrapolations, e.g.
  1) In vitro toxicity screens are not metabolically competent and limited to few cell types.
  2) In vivo risk assessment overly-dependent upon parent drug level in plasma comparisons and under-served by basic information on species-specificity.
  3) Accumulation in cells/tissues and/or organs.
- What about other factors e.g. protein binding, cell transporter that might impact disposition and which are the most important exposure parameters to consider: Cmax v's AUC for thinking about safety margins in a genetox context and how does MOA (direct versus indirect) impact this?
- What would be needed to more efficiently move forward?

e. *11:00 am – 11:35 am*
Lunch

3. *11:35 am – 2:00 pm*
***Session III*: The Use of Quantitative Approach of Genotoxicity for Risk Assessment**
Session Chair: Paul White (Health Canada, Canada)

a. *11:35 am – 12:00 pm*
Can In Vivo PoD Estimates for Genotoxicity Inform Carcinogenic Potency? Lya Soeteman-Hernandez (RIVM, Netherlands)

b. *12:00 pm – 12:25 pm*
The Use of Dose Response Data for Risk Assessment – Diane Benford (Food Standards Agency, UK)

c. *12:25 pm – 12:50 pm*
The COSMOS Project: Developing *in Silico* Models to Support *in Vitro* Approaches to Ultimately Predict *in Vivo* Toxicity – Mark Cronin (Liverpool John Moores University, UK)

d. *12:50 pm – 1:15 pm*
   CAAT Perspectives on In Vitro to In Vivo Extrapolations - Thomas Hartung (Johns Hopkins University, USA)
e. *1:15 pm – 1:45 pm*
   Panel Discussion

   Discussion Questions:

   - Is the regulatory community ready to accept/use quantitative metrics derived from in vivo genetic toxicity dose-response data to set regulatory limits and assess human hazard/risk (i.e., as opposed to cancer endpoints)? If not, what are the barriers? Would different methods/approaches be applied to germ- and somatic cell data?
   - Have in silico and/or in vitro-to-in vivo extrapolation methods matured to the point where they can effectively be deployed in a regulatory setting? If not, what hurdles need to be overcome?

f. *1:45 pm – 2:00 pm*
   Concluding Remarks
g. *2:00 pm*
   End of the main meeting
h. *2:45 pm*
   Departure of coach bus to Manchester airport *(advanced ticket purchase required through the GTTC Workshop registration system).*

SPEAKER ABSTRACTS

THURSDAY, 10 JULY 2014

Plenary Lecture I: PK and PD Tools for DNA-Damage Pathways: Modeling Dose Metrics and DNA-Repair Processes

Mel Andersen, The Hamner Institutes, USA

Advances in analytical chemistry and in cellular imaging provide enhanced tools to evaluate dose response of DNA adduction and of DNA-repair processes following treatment with DNA-damaging compounds. The combination of these approaches has accelerated efforts to understand the dose response of damage-repair and provided better mechanistic underpinning for threshold behaviors with mutation and DNA-damage – endpoints for which linear low-dose risk assessment models have prevailed since the 1970's. This presentation first focuses on lessons learned from Hamner staff efforts to develop cellular PK models for formaldehyde – a DNA-damaging compound that is a byproduct of several metabolic pathways in every cell - and to use these PK models to assist in interpreting formaldehyde-DNA reaction products from endogenous and exogenous formaldehyde in rats (e.g., Swenberg et al., Tox.Sci., 120, S130-S145, 2011). Enhanced LC-MS analytical tools have allowed determination of levels of DNA-reaction products in nasal epithelium. Increased cancer in rat nose occurs where exogenous DNA-formaldehyde reaction products are still lower than are those formed by endogenous metabolism. By what mechanisms do cells deal with a significant background of DNA-reaction products without adverse consequences? The presentation then examines this question by looking at data sets and computational models developed at The Hamner on the manner in which cells respond efficiently to low levels of damage and insure that small increases in damage do not increase the risk of heritable changes during replication. We have examined diverse responses to prototypical DNA-damaging compounds , including etoposide (ETP) and neocarzinostatin (NCS), in HT1080 cells examining whole genome gene expression, high content imaging of DNA-damage markers (γH2AX and p53), semi-quantitative measures of key phosphoproteins (ATM, ATR, p38, Chk2, and p53), micronuclei (MN) and formation of DNA-repair foci. Transcriptional upregulation of repair, cell cycle and apoptosis genes only occurred at doses causing with clear increases in MN formation. On the other hand, repair foci formation, occurring at lower concentrations than MN formation, appears to be responsible for modulating responses to low levels of DNA-damage for chemicals such as NCS that show threshold

responses for DNA-damage, in this case MN formation. The talk ends with a discussion of cell signaling modules that can produce threshold behaviors and outlines studies needed to determine the repair modules at work with various forms of DNA-damage.

IWGT Workgroup Recommendations for Quantitative Assessment of Dose-Response in Genetic Toxicology

George Johnson, Institute of Life Science, College of Medicine, Swansea University, Swansea, UK

The presentation summarizes the discussion and conclusions of the IWGT Working Group on Quantitative Approaches to Genetic Toxicology Risk Assessment (IWGT QWG) that met in Foz do Iguaçu, Brazil October 31-November 2, 2013. Topics addressed included 1) the need for quantitative dose-response analysis, 2) methods to analyze exposure-response relationships & derive point of departure (PoD) metrics, 3) PoDs and mechanistic threshold considerations, 4) approaches to define exposure-related risks, 5) empirical relationships between genetic damage (mutation) and cancer, and 6) extrapolations across test systems and species. The working group critically examined PoD metrics that could be used to define low-dose risk of genetic damage and from which extrapolation to acceptable exposure levels could be made using appropriate mode of action information and uncertainty factors. These included benchmark doses (BMDs) derived from fitting families of exponential models, the no genotoxic effect level (NOGEL), and “threshold” or breakpoint dose levels derived from bilinear models (Td or BPD; dose below which there is no statistically significant increase) when mechanistic data supported this approach.

The WG concluded that, since neither experimentation nor mathematical analysis can definitively exclude small genotoxic effects within the normal background range, it is not productive to argue about the existence of thresholds for mutagenic and clastogenic agents. Rather, emphasis should be placed on determination of PoD values from which acceptable exposure levels can be determined by extrapolation using available mechanistic information and appropriate uncertainty factors. This approach places the focus on minimization of genotoxic risk, which necessarily protects against the risk of the development of diseases that would result from the genetic damage.

The WG concluded that the order of preference of PoD metrics is the statistical lower bound on the BMD>the NOGEL>a statistical lower bound on the BPD. Scaling and uncertainty factors that require consideration for extrapolation below the PoD and/or across test systems and/or to humans include species differences in absorption, distribution, metabolism, excretion, and pharmacokinetics, severity of effect, differences in repair capacity, inter-individual differences, and study factors such as duration of exposure. Analysis of the correlation between selected genetic damage endpoints (i.e., mutation and chromosomal aberrations) and cancer, suggests that quantitative analysis has the potential to improve cancer risk assessment and to protect against key genetic events that may lead to cancer. Although the genotoxic potency of selected carcinogens is empirically related to carcinogenic potency, very few genotoxicity data sets are matched with respect to species, strain, and tissue in which cancer has been experimentally observed. More tissue-matched data is needed to support increased reliance on quantitative correlations between genetic toxicity and carcinogenicity.

A Toolbox to Estimate Point-of-Departure Metrics in Genetic Toxicology

Paul White, Environmental Health Science and Research Bureau, Health Canada, Ottawa, Canada

Interpretations of genetic toxicity test results have traditionally involved dichotomous hazard identification (i.e., positive versus negative) rather than quantitative dose-response analyses and point-of-departure (PoD) determination. Recent work conducted under the auspices of the ILSI/HESI Genetic Toxicology Technical Committee (GTTC) has established a foundation for routine dose-response analyses and PoD determination. GTTC members collected and analyzed dose-response data for four potent alkylating agents across a wide range of in vitro and in vivo endpoints and evaluated various techniques for PoD determination. Routine PoD determination necessitated the development of a standardized analytical methodology. The initial work (Gollapudi et al., 2013), which examined dose-response data for MMS (methyl methane sulfonate) and EMS (ethyl methanesulfonate), employed published methods to determine PoDs such as the no-observed-genotoxic-effect-level (NOGEL), the breakpoint-dose (BPD; previously Td), and the benchmark dose (BMD). Subsequent analyses of data for ENU (1-ethyl-1-nitrosourea) and MNU (1-methyl-1-nitrosourea) (i.e., Johnson et al., 2014) expanded the range of analytical tools via inclusion of two R-based procedures for bilinear analysis (i.e., segmented) and non-linear smoothing (i.e., mgcv). An R-based tool called drsmooth, which is now available through CRAN (Comprehensive R Archive Network), and a companion guidance document, were created to facilitate routine analyses of dose-response data and derivation of numerous PoDs. The Guidance Document contains complete instructions regarding initial data screening and processing (e.g., requirements for transformations), installation of required R-based tools, and determination of PoDs via drsmooth (i.e., NOGEL, BPD, BMD and STD). The drsmooth package includes analytical tools to examine variable distributions and variance homogeneity, statistical tools for NOGEL determination, and analytical tools for dose-response "shape testing" and subsequent modelling to determine BPD, STD and BMD. BPD determinations employ two modelling techniques, the Lutz and Lutz "hockey-stick" approach and the R-based segmented procedure. Similarly, BMD determinations employ two non-linear modelling tools, BMDS (USEPA) and PROAST (RIVM).

Biological Processes Driving the Response to Low Doses

George Johnson, Institute of Life Science, College of Medicine, Swansea University, Swansea, UK

In early 2000, a paradigm shift was initiated, where certain classes of genotoxic substance were accepted by regulatory bodies as having sub-linear dose responses. This new approach, which deviated from the default linear method, was based on mode of action (MOA). Substances known to cause genetic damage through a non-DNA reactive mechanism were shown to have points of departure (PoD), where low levels of the substance were tolerated through biological processes. Since that time, there has been an increasing body of evidence to show that certain DNA reactive substances also produce sub-linear dose responses with clear PoD metrics. It has long been known that DNA repair has a major effect on genetic toxicity dose responses, however to clearly link this MOA to the PoD, the assay, study design and statistical approach must all be suitable for PoD analysis. We have addressed this by assessing the effects of specific DNA repair enzymes on dose responses of model alkylating agents e.g. EMS and MNU, using standard mammalian cell based genotoxicity tests. These enzymes have been

shown to be up-regulated by low doses of alkylating agents, and furthermore by knocking down specific DNA repair enzymes, the PoD metrics are reduced considerably. In conclusion, DNA repair has been shown to be a MOA for the PoD exhibited by mono-functional alkylating agents, and further work is required to define similar mechanisms that influence the PoD for other classes of DNA reactive substance.

Application of the TT21C Strategy to Safety Assessment for DNA Damaging Compounds Using Quercetin as a Case Study

Rebecca Clewell, The Hamner Institutes, USA

The National Academies of Sciences 2007 report, "Toxicity Testing in the 21st Century (TT21C): A Vision and A Strategy" called for a change in toxicity testing, focusing on evaluating changes in normal cellular signaling pathways using human-relevant cells rather than relying on high dose animal studies. To support this transition, our laboratory is working to provide practical examples of how the TT21C vision can be implemented to facilitate chemical safety assessments for several toxicity pathways, including the DNA damage response pathway. The project studies p53-mediated DNA damage stress response in human cells to determine the underlying response circuitry and the dose-response behavior for pathway activation, and adverse outcomes, after chemical induced DNA damage. This research effort has three overarching goals: (1) map the key determinants of cellular fate following DNA damage by chemicals with different mechanisms of action, (2) identify dose-dependent thresholds associated with adaptation and toxicity (mutation) and (3) perform a risk assessment for prototype chemicals based on predicted regions of safety. Initial work involved validation of the in vitro model and collection of dose-response data at the gene (transcriptomics), protein (p53, p-p53, p-H2AX, MDM2, etc.), and cellular (cell cycle arrest, apoptosis, micronucleus) level using prototype chemicals for DNA damage: etoposide, methylmethane sulfonate and quercetin. In concert with data acquisition and pathway inference, a computational systems biology pathway (CSBP) model is being developed to quantitatively describe the p53 network in order to calculate dose-response behaviors and predict regions of safety (no net increase in adverse cellular outcome). Biokinetic models will then be used to facilitate in vitro-in vivo extrapolation (IVIVE) and the determination of safe levels of human exposure from in vitro and CSBP results. This presentation describes the current progress in an ongoing research effort aimed at providing a proof-of-concept, pathway based, in vitro-only safety assessment for the prototype chemical quercetin.

Qualitative and Quantitative Approaches on the Threshold of Genotoxic Carcinogens

Shoji Fukushima[1], Min Gi[2], Anna Kakehashi[2] and Hideki Wanibuchi[2]
[1]Japan Bioassay Research Center, Japan Industrial Safety & Health Association, Hadano, Japan; [2]Department of Molecular Pathology, Osaka City University Graduate School of Medicine, Osaka, Japan

Chemical carcinogenesis is composed of multistep process (initiation-promotion-progression). Genotoxic carcinogens which are DNA-reactive, induce DNA adduct formations and genetic alterations in target cells, resulting in generation of mutated cells (initiation). Preneoplastic lesions appear through clonal proliferation of the mutated cells and transform into tumor

developments (promotion). Many factors may influence these processes in a dose-response manner. Therefore, qualitative and quantitative low dose-response analysis is an important theme in research of carcinogenic threshold of the genotoxic carcinogens. Herein, we present results of low-dose carcinogenicity studies of the genotoxic carcinogens based on medium-term carcinogenicity bioassay for carcinogens, and relationship between carcinogenesis-related key events and their deriving point of departure (PoD). Their PoDs also were compared to those of carcinogenic induction. In a case with a hepatocarcinogen, 2-amino-3,8-dimethylimidazo(4,5-f)quinoxaline (MeIQx), a rat liver exposed to the carcinogen was examined to determine the formation of MeIQx-DNA adducts, formation of mutations at LacI transgene, initiation activity and inductions of preneoplastic glutathione S-transferase placental form (GST-P)-positive foci. Their BMDs obtained from above key events were increased along advance of the carcinogenesis step and were lower than that of cancer induction. The order of significant induction of the key events was: formation of DNA adducts $\rightarrow$ Mutations, initiation activity $\rightarrow$ GST-positive foci $\rightarrow$Similar data on genotoxic and carcinogenic PoDs were obtained for hepatocarcinogens such as 2-amino-3, 8-dimethylimidazo(4,5-f)quinoline and N-diethylnitrosamine, and colon carcinogen, 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine. These results contribute to an answer of issue on existence of the genotoxic carcinogenic threshold, although the data might be still limited.

Benchmark Dose for Genetox and Cancer Endpoints and Correlating between Systems

Wout Slob, Center for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Qualitative hazard evaluation (identification) assumes that effects are either present or absent. The latter assumption may be regarded as a reduction of an underlying quantitative phenomenon, where effects vary in magnitude. The implication is that a quantitative approach of hazard identification is more adequate, even for situations where yes/no answers are needed (e.g. for regulatory purposes). This transition to a quantitative approach demands a change in thinking regarding a number of fundamental principles, such as: measuring zero effects in experimental science, using a threshold defined as a dose without any effect, or, drawing conclusions based on the question “do we see an effect or not?”. The way of estimating (e.g. genotoxic or carcinogenic) potencies of chemicals is by estimating BMDs (Benchmark doses). The BMD approach allows for quantifying the precision in the BMD estimate by a confidence interval, which is essential information. For datasets that are relatively poor the confidence interval may be quite wide, in some cases unbounded. Using the recent finding that the shape of dose-responses among chemicals (for a given endpoint) tend to be homogenous, the precision of BMD estimates derived from individual datasets can be substantially improved by a sort of read-across approach. By applying the BMD approach to the dose-response data of two different systems (e.g. carcinogenicity vs. genotoxicity) for many chemicals, the potency estimates for both systems can be correlated to each other. When a positive correlation is found the potency of one system can be used to predict that of the other for a chemical lacking data on the latter.

An update from the UK Industrial Genotoxicity Group (IGG) on Work of In Vitro Risk Assessment

Ann Doherty, AstraZeneca, UK

In recent years the IGG meetings have showcased a number of examples of in vitro risk assessment in both its annual meeting and in its data workshops. In this session we provide in vitro data from the pharmaceutical industry and bench mark dosing that we conducted alongside the in vivo testing. For a compound series with anuegenic activity in the in vitro micronucleus assay we have experienced some cases where we could fit the model to bench mark dose using PROAST and other compounds where we could not. We can also compare these data and BMD10 to the in vivo micronucleus data ultimately seen.

Other industry groups are also using quantitative genotoxicity data to add weight of evidence to risk assessments. The cosmetics and personal care industries have presented data at IGG meetings using POD/BMD10 to explore the concept of exposure based risk assessment for Quercetin as a biologically relevant anchor for mechanistic toxicity pathway data (unilever data www.TT21C.org).

FRIDAY, 11 JULY 2014

Plenary Lecture II: Level of concern for genotoxic carcinogens at human relevant exposure

Alan Boobis, Peter Craig, Villi Flari, Andy Hart, Lesley Rushton, Ehi Idahosa-Taylor and HESI RISK 21 Committee
Department of Medicine, Imperial College London, London, UK

A number of authorities, including the WHO, have recommended use of the Margin of Exposure (MOE) for ranking and prioritising risks from genotoxic carcinogens. The MOE is the ratio of a point of departure for tumour induction to an estimate of human exposure. There is currently no consensus on the scientific basis for interpreting the level of concern associated with a given MOE. This has now been explored using a number of complementary lines of evidence, including expert elicitation, analysis of published "mega" studies, comparison of animal and human data for known human carcinogens and comparison of upper bound risk in humans for animal carcinogens not known to be carcinogenic in humans. This analysis revealed considerable uncertainty and that it was not possible to explore empirically the dose-response at the risk level of concern. In an effort to produce a novel means of communicating and evaluating the MOE, the HESI RISK21 project has developed a tiered approach to both exposure and hazard assessment, the outputs of which are plotted as either ranges or distributions, on a risk matrix (RISK21 matrix). Comparison of the relative MOEs of different compounds or exposure scenarios is readily achieved, as is identification of the best strategy for risk reduction. Interpretation of relative risk can take into account modifying factors such as mode of action and toxicokinetics. The RISK21 matrix is available as a free-to-use online web tool.

Integration of Dosimetry and Exposure into In Vitro High-Throughput Screening
Amin Rostami-Hodjegan, Professor of Systems Pharmacology, Faculty of Medical and Human Sciences, University of Manchester & Vice President of R&D at Simcyp (a Certara Company), UK

The ability to accurately predict the in vivo clearance of a compound is of key importance in determining the internal exposure (based on the 'Area Under the Curve' [AUC] of the concentration of the chemical circulating in the blood stream) following external exposure [Dose]. Additional elements defining the AUC following a certain 'dose' are the route of entry to the system (dermal, inhalation, oral ingestion) and the bioavailability associated with each of route.

Knowledge of the extent of metabolism of a drug and its inter-individual variability are essential for estimation of population variability in AUC and hence potential toxicity. There are now battery of in vitro assays (e.g. cell cultures, recombinantly expressed cell lines or human tissue sub-fractions) which enable some initial assessment of a concentration-(toxicity)-response between a given xenobiotic and the host systems. However, a realistic incorporation of inter-individual variability into extrapolating practice requires the knowledge of the correlations between abundance (/activity) of various enzymes.

Although creating virtual populations for the toxicological assessment of chemicals has become popular using the framework of Monte-Carlo simulations, currently these simulations do not consider correlations between abundance of enzymes. We have recently established correlations between various enzyme abundances in 24 individual liver samples using a multiplexed QconCAT LOCMS method (Achour et al, 2014, Drug Metab Dispos, 42, 500-510). This has produced a correlation matrix for the first time which can be used to generate more realistic virtual populations with respect to abundance of various enzymes and hence a better simulation of population variability when linking dose to AUC.

Computational Tools and Models to Facilitate In Vitro to In Vivo Exposure Extrapolation – Lessons from the Drug Development World
Oscar Della Pasqua, University College London, UK

Failure to predict side effects at early stages of drug development has led to the withdrawal of several drugs from the market over the last decades. Such safety findings raise questions about the predictive value of the data generated to support the approval process and most importantly whether knowledge is being integrated in an effective manner. In this presentation pharmacokinetic-pharmacodynamic (PKPD) modelling is introduced as a pharmacological, mathematical and statistical tool for risk assessment. Based on real-life examples, we show how a mechanism-based approach can be developed to establish the predictive value of data correlations. Its use in pharmaceutical R&D has evolved together with the availability of applications of information and communications technology (ICT), which has become imperative in different stages of the drug discovery and development pipeline (see Figure 1).

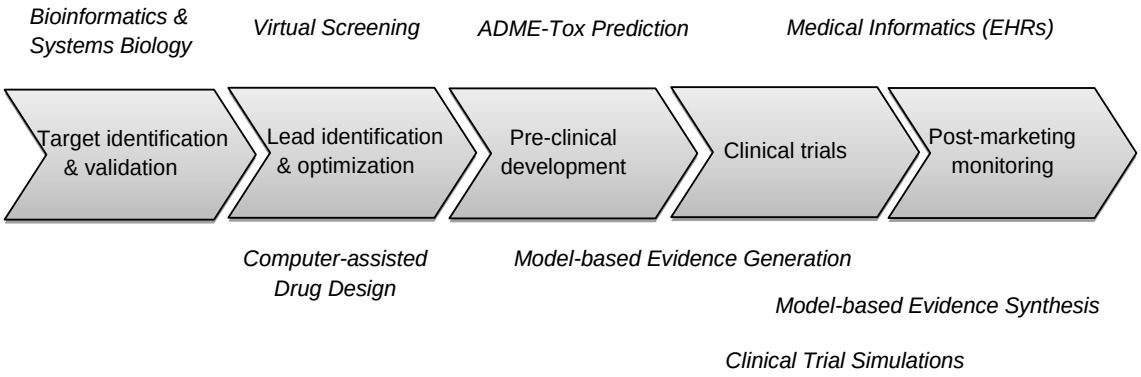


Figure 1. Examples of computational tools and knowledge management principles supported by information technology across the pharmaceutical R&D pipeline.

Our analysis reveals that despite the developments in quantitative pharmacology current approaches in non-clinical, clinical and surveillance research are limited to descriptive methods, which disregard underlying pharmacokinetic-pharmacodynamic relationships. Irrespective of the availability and uptake of novel methodologies for early detection of risk, there is lack of a quantitative framework that allows for interspecies scaling as well as translation of findings across different dimensionalities, i.e., from in vitro to in vivo, from animal to human, from health to disease, from short to long term. A shift is required in the way translational research is performed to ensure that data generated in the different pharmaceutical R&D phases take into account the need to characterize exposure-response relationships.

Reverse PB/PK Dosimetry for Extrapolation of Biomonitoring
George Loizou, Health and Safety Laboratory, UK

Exposure reconstruction from biomonitoring (BM) data using reverse dosimetry and physiologically based toxicokinetic (PBTK) models should in theory reduce uncertainty and variability by constraining variability to within physiologically feasible ranges. However, the utility of the PBTK approach depends on the accuracy of the model used to describe the biological system it represents. In this presentation the results from a study will be presented where a range of PBTK models, with increasing levels of biological detail, were used to simulate data generated from laboratory based human volunteer studies where both the BM outputs and the exposure are known. Comparisons were made between predicted and actual data to assess the ability of the models to reconstruct exposure. A workflow will be described where global sensitivity analysis (SA) of the models was used to identify; 1) the most important parameters that determine uncertainty and variability in BM data, 2) how the information was used to reduce the number of model parameters with minimal loss of precision in the estimation of exposure, 3) how this significantly reduces the computational cost of these simulations and, 4) how this type of analysis has the potential to inform the prioritization of resources in BM field studies.

Can In Vivo PoD Estimates for Genotoxicity Inform Carcinogenic Potency?

Lya G. Soeteman-Hernández[1], Jan van Benthem[1], Dan Levy[2], Kristine L.Witt[3], Wout Slob[4]

[1]Center for Health Protection, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; [2]U.S. Food and Drug Administration, Maryland, USA; [3]National Institute of Environmental Health Sciences, Division of the National Toxicology Program, Research Triangle Park, North Carolina, USA; [4]Center for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

We investigated the applicability of using *in vivo* mouse micronucleus (MN) data to derive cancer potency information. The dose-response modeling program PROAST was used to calculate benchmark doses (BMDs) for estimating the genotoxic and carcinogenic potency for 51 compounds: 41 were studied by the National Toxicology Program (NTP) for induction of MN and carcinogenicity, and 10 were analyzed from published studies. BMD_{05}s (for a 5% increase in MN counts) were derived from MN data, and BMD_{10}s (for 10% extra risk) were derived for carcinogenicity data in mice, along with their respective upper (BMDU) and lower (BMDL) confidence intervals. For each compound, the lowest BMD from all the available studies was selected for further analysis. Both genotoxicity and carcinogenicity data showed high variability in estimated BMDs for the same compounds when datasets derived under different study conditions were compared. Our data showed a clear correlation between the lowest tumor $BMDL_{10}$ and the lowest *in vivo* MN $BMDL_{05}$. Previously, MN data were thought to provide only a qualitative indication of carcinogenicity. Results suggest that measurement of genetic damage in erythrocytes may be used to estimate carcinogenic potency as well. Overall, these results suggest that the MN $BMDL_{05}$ would provide a conservative estimate of the tumor $BMDL_{10}$. Given that most of the NTP studies used a13-week exposure duration, further research is needed to determine whether shorter term studies can also be used to predict cancer potency, and whether refining lesion categories leads to improved potency correlations.

The Use of Dose Response Data for Risk Assessment

Diane Benford, Food Standards Agency, UK

Genotoxic substances are generally not permitted for deliberate use in food production. However an appreciable number of known or suspected genotoxic substances occur unavoidably in food, e.g. from natural occurrence, environmental contamination, generation during cooking and processing. Acrylamide, aflatoxins, arsenic, chloropropanols, ethylcarbamate, formaldehyde, heterocyclic amines, nitroso compounds and polycyclic aromatic hydrocarbons are just a few examples of carcinogenic contaminants that are present in some foods.

Over the past decade a margin of exposure (MOE) approach has increasingly been used in assessing the exposure to substances in food that are genotoxic and carcinogenic. The margin of exposure is defined as a reference point on the dose-response curve (e.g. a benchmark dose lower confidences limit derived from a rodent carcinogenicity study) divided by the estimated human intake. A small margin of exposure indicates a higher concern than a very large margin of exposure. Whilst the margin of exposure cannot be directly equated to risk, it supports

prioritisation of substances for further research or for possible regulatory action, and provides a basis for communicating to the public.

So far, the MOE approach has been confined to substances for which carcinogenicity data are available. In the absence of carcinogenicity data, evidence of genotoxicity is used only in hazard identification. The challenge to the genetic toxicology community is to develop approaches for characterising risk to human health based on data from genotoxicity studies.

The COSMOS Project: Developing in Silico Models to Support in Vitro Approaches to Ultimately Predict in Vivo Toxicity

Mark Cronin, School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool, England

The COSMOS Project (www.cosmostox.eu) is a major European Initiative and part of the SEURAT-1 Cluster (www.seurat-1.eu). The COSMOS Project aims to develop computational approaches to assist in the prediction on in vivo repeated dose toxicity. The major efforts have resulted in the creation of the COSMOS database of more than 12,000 toxicity studies across 27 endpoints for more than 1,600 compounds; an update of the Threshold of Toxicological Concern (TTC) focussing on cosmetics ingredients; development of in silico (QSAR, category formation and read-across) models; and to support quantitative in vitro – in vivo extrapolation. A number of open sources software tools have been developed to simulate long-term exposure to chemicals and assess human bioconcentration factor. Physiologically-Based ToxicoKinetic (PBTK) models have been calibrated and refined to account for uptake in different tissues (GI tract, skin, lungs). This methodology was supplemented with QSAR models to predict hepatic clearance. Adverse Outcome Pathways (AOPs) are seen as one method, in terms of a framework to organise information, to support the use of in vitro toxicity to predict in vivo effects. The research leading to these results has received funding from the European Community's 7th Framework Program (FP7/2007-2013) under grant agreement n° 266835 and from Cosmetics Europe.

CAAT Perspectives on In Vitro to In Vivo Extrapolations

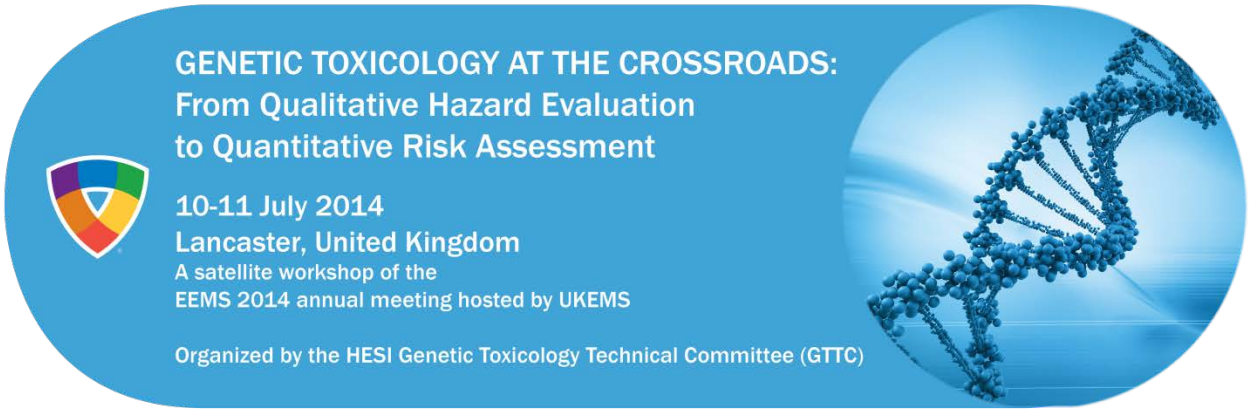
Thomas Hartung, Johns Hopkins University, USA

Quantitative In Vitro to In Vivo Extrapolations (QIVIVE) is broadly considered a prerequisite to bridge from in vitro findings to a dose paradigm. CAAT has steered a roadmap exercise for animal-free systemic toxicity testing (Basketter et al., 2012, ALTEX 29:3-89), where the needs and opportunities for toxicokinetics were elaborated in the context of the different systemic toxicities. The report was discussed in two stakeholder fora in Brussels 2012 and Washington 2013; the key recommendations will be summarized.

However, contrary to common believe and the Paracelsus paradigm, the majority of industrial chemicals is not showing a given health effect. Thus, strengthening the credibility of negative results of alternative approaches for hazard identification avoids the need for QIVIVE. Here, especially the combination of methods in Integrated Testing Strategies is most promising.

Two further – very much opposite - approaches aim to overcome the problem of modeling in vivo complexity: The Human-on-chip movement initiated by NIH/FDA/DARPA and DTRA in the

US, aims to reproduce large parts of body complexity with microphysiological systems, i.e. organ equivalents combined by microfluidics. At the same time, the Toxicity Testing in the 21st Century (Tox-21c) movement aims for mechanistic approaches (Adverse Outcome Pathways as promoted by OECD or Pathways of Toxicity of the Human Toxome project) to be used for high-throughput screening, biological phenotyping and ultimately a Systems Toxicology approach by integration with computer modeling. Noteworthy, these 21st century approaches require also 21st century validation. A case is made that evidence-based toxicology, i.e. translating evidence-based medicine to toxicology, can help here.



SPEAKER BIOGRAPHIES

Melvin (Mel) Andersen, PhD
Dr. Melvin Andersen is the Chief Science Officer and Director of the Institute for Chemical Safety Sciences at The Hamner Institutes for Health Sciences, in Research Triangle Park, NC. His career-spanning research on the pharmacokinetics and pharmacodynamics of environmental chemicals and drugs has emphasized the importance of computational modeling approaches for improving dose response evaluations and safety assessments. He has published over 400 peer-reviewed papers and book chapters in areas of toxicology and risk assessment. Many of the current research programs at The Hamner focus on implementing toxicity testing approaches outlined in the 2007 NAS report, "Toxicity Testing in the 21st Century: A Vision and A Strategy" through the use of case studies with specific toxicity pathways (www.thehamner.org/tt21c). One of the Hamner case studies examines the mechanistic bases for thresholds in the p53-mdm2 DNA damage pathways with various compounds. With various collaborators, he has also developed PK models that relate levels of tissue formaldehyde with dose-dependent modes-of-action through analysis of altered gene expression in nasal epithelium. He did a PhD in biochemistry and molecular biology in 1971.

Diane Benford, BSc, PhD
Dr. Diane Benford is head of the Chemical Risk Assessment Unit at the UK Food Standards Agency. The Unit has overall responsibility for advice on possible adverse human health effects of all types of chemicals in food, but much of Diane's work focuses on contaminants, food additives and natural toxicants. The Unit's advice is based on scientific risk assessments and underpins the Agency's policy work and advice to consumers. Diane's role at the Food Standards Agency also includes acting as scientific secretary to the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) and part of the joint secretariat to its sister committee on Mutagenicity (COM) and Carcinogenicity (COC). In a personal capacity, Diane has been a member of the scientific panel on contaminants in the food chain [CONTAM] of the European Food Safety Authority (EFSA) since 2005, and is currently chair of the panel. Since 2001 she has participated in meetings of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). She previously chaired an ILSI Europe expert group on the margin of exposure approach to substances in food that are genotoxic and carcinogenic.

Prof. Alan R Boobis OBE, PhD, CBiol, FSB, FBTS

Alan Boobis is professor of biochemical pharmacology in the Department of Medicine, Imperial College London and Director of the Public Health England Toxicology Unit. He has been a member of Imperial College London (initially at the Royal Postgraduate Medical School) for almost 40 years. His main research interests lie in mechanistic toxicology, drug metabolism, toxicity pathway analysis and increasingly over the last 20 years or so, in the application of knowledge in these areas to risk assessment. He has published around 230 original research papers and has served as an Editor-in-Chief of Food and Chemical Toxicology. He is or has been a member/chair of a number of national and international advisory committees involved in the risk assessment of chemicals, including human and veterinary drugs, pesticides, chemical contaminants and atmospheric pollutants. He is a fellow of the Society of Biology and of the British Toxicology Society. He has served as president of Eurotox and received the Merit Award in 2009. He is a past chair of the British Toxicology Society and received the John Barnes Prize Lectureship in 2013. He is a recipient of the Royal Society of Chemistry Toxicology Award. He was awarded an OBE in 2003.

Rebecca Clewell, PhD

Rebecca Clewell is a research investigator at The Hamner Institutes for Health Sciences in North Carolina, USA. Rebecca received her B.S. and M.S. in Chemistry from Wright State University in Ohio and her Ph.D. in Environmental Science and Engineering from the University of North Carolina at Chapel Hill. Rebecca's research focuses on developing in vitro and in silico tools that will aid in the interpretation and replacement of animal-based toxicity studies. By collecting and integrating data on chemical dose-response, pharmacokinetics, and mechanisms of action, she seeks to characterize both target chemical dose and biological effect across doses. She is currently leading The Hamner's Toxicity Testing in the 21st Century (TT21C) laboratory efforts, which are focused on the DNA damage, oxidative stress, estrogen receptor and peroxisome proliferator activated receptor toxicity pathways.

Prof. Mark Cronin

Mark Cronin is Professor of Predictive Toxicology at the School of Pharmacy and Chemistry, Liverpool John Moores University (LJMU), Liverpool, England. He has over 25 years expertise in the application of *in silico* approaches to predict the toxicity and fate of chemicals; in addition to development of strategies (such as integrated testing strategies) to develop alternatives to whole animal testing for toxicity. Research in recent years has centred on the application of these alternatives for regulatory use (e.g. classification and labelling; prioritisation; data gap filling) and for product development and regulatory risk assessment. Current research includes the application of chemical grouping and read-across to assess human health and environmental endpoints, particular the linking of the Adverse Outcome Pathways (AOPs) to category formation. This research effort has resulted in four books and over 200 publications in all areas of the use of (Q)SARs, expert systems and read-across to predict toxicity. He has worked in numerous projects in this area including more than ten EU Framework Projects as well as assisting in the uptake of *in silico* methods for regulatory purposes. He co-ordinates the EU COSMOS Project which is part of the SEURAT-1 Cluster.

Oscar Della Pasqua, PhD
Dr. Oscar Della Pasqua is the Senior Director Clinical Pharmacology Modelling & Simulation at GlaxoSmithKline, United Kingdom and Professor Chair Clinical Pharmacology & Therapeutics at the School of Life and Medical Sciences, University College London. In addition to his extensive experience in early and late clinical development, he leads a research group focused on biomarkers, disease modelling and clinical trial design methodology, which has resulted in more than 75 publications in clinical and scientific journals. Dr. Della Pasqua chairs the Medicines for Children Advisory Network (MCAN), an internal expert panel at GlaxoSmithKline and is also a member of the Global Research in Paediatrics (GRiP) Network of Excellence, where he coordinates the efforts on novel methodologies for the evaluation of paediatric efficacy and safety data. He represents GlaxoSmithKline in different IMI (Innovative Medicines Initiative) consortia aimed at the evaluation of efficacy and safety of novel medicines. Since 2008 he holds an affiliate lecturer position at the University of Cambridge where he contributes the Clinical Pharmacology module in Translational Medicine and Therapeutics (TMAT).

Ann Doherty, PhD
Ann Doherty is currently Director of Genetic Toxicology Group at AstraZeneca. Ann gained her PhD in Genetic Toxicology on the *in vitro* micronucleus test in 1995 from Swansea University supervised by Elisabeth Parry. Ann then completed post-doctoral projects at Swansea University (non-disjunction seen with the aneugen trichlorofon) and University of Leicester (antibody localisation in SLE) and a research fellowship at University of Bristol (Chromosomal translocations detected by FISH in patients with metal on metal hip replacements). In 2002 Ann joined Genetic Toxicology group at AstraZeneca in Alderley Park to lead the cytogenetics team and has developed within AZ to Director for Genetic Toxicology group in 2013. Ann is currently the chair of the UK Industrial Genotoxicity Group (IGG) and, former Secretary, she is also a UK Environmental Mutagen Society (UKEMS) committee member representing IGG, and represents AstraZeneca on EFPIA as Comet Group member. Ann Doherty has strong links with the Genetic Toxicology Group at Swansea co-supervising two BBSRC funded PhD students with AZ CASE awards. In January 2014 Ann was awarded an honorary Professorship at Swansea University.

Shoji Fukushima, MD, PhD
Dr. Shoji Fukushima is the Director of the Japan Bioassay Research Center, Japan Industrial Safety and Health Association. He started in 1968 as a lecturer in the Department of Pathology, Nagoya City University Medical School and became an Associate Professor in 1980. He was a Professor at the Department of Pathology from 1990-2006 at the Osaka City University Medical School, and served as the Dean in Osaka City University Medical School from 2002-2006. He then became the Director at Japan Bioassay Research Center in 2006. Dr. Fukushima's research interests include chemical carcinogenesis, cancer risk assessment, and pathology of the urinary bladder. He has served on the Editorial Board of Cancer Letters, Cancer Science, Pathology International, and the Japan Journal of Clinical Oncology in the past and present.

Thomas Hartung, MD, PhD

Thomas Hartung, MD, PhD, is Professor of Toxicology (Chair for Evidence-based Toxicology), Pharmacology, Molecular Microbiology and Immunology at Johns Hopkins Bloomberg School of Public Health, Baltimore, and University of Konstanz, Germany; he also is Director of their Centers for Alternatives to Animal Testing (CAAT, http://caat.jhsph.edu) with the portal AltWeb (http://altweb.jhsph.edu). CAAT hosts the secretariat of the Evidence-based Toxicology Collaboration (http://www.ebtox.com) and the industry refinement working group. As PI, he heads the Human Toxome project (http://humantoxome.com) funded as an NIH Transformative Research Grant. He is the former Head of the European Commission's Center for the Validation of Alternative Methods (ECVAM), Ispra, Italy. He has authored more than 400 scientific publications.

George Johnson, PhD

Dr. George Johnson is an Associate Professor in the Institute of Life Science at Swansea University, UK. George obtained his PhD degree in Swansea 2006, under supervision of Professor Jim Parry, and since then has developed a great interest in the statistical approaches and underlying mechanisms that support points of departure (PoD) for genetic toxicity. This expertise has lead George to being a Steering Member of the International Life Science Institute – Health and Environmental Science Institute (ILSI-HESI) Genetic Toxicology Technical Committee (GTTC) http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3330 as well as being co-Chair of the GTTC 'Quantitative Workgroup'. His work includes improving the quantitative use of genetic toxicity data for human-health risk-assessment (Johnson et al., 2014, EMM), and he links this to his great interest in replacing, reducing and refining (3Rs) the use of animals in research. His current projects include a joint GTTC, RIVM, Swansea, Health Canada collaboration that is funded through Health Canada's chemical management programme (Prof. Paul White as PI) as well as collaborations on the effect of background mutation frequencies on PoDs with US-FDA-NCTR (Cao et al., 2014, EMM), assessing genetic toxicity profiles of drug candidates with the Drugs for Neglected Disease Initiative, in-vitro to in-vivo correlations with the National Institute for Public Health and the Environment (RIMV, Netherlands) and Astra Zeneca, the International Workshop on Genetic Toxicology Quantitative Workgroup 2013, developing and testing high-throughput high-content flow cytometry based genetic toxicology assays with GSK, Gentronix, Litron, and Hoffman-La-Roche, developing an in vitro cancer assay with the National Centre for 3Rs of animal testing (NC3R) and GE Healthcare, along with being involved in numerous projects with the DNA Damage group in Swansea University http://www.swansea.ac.uk/medicine/research/a-zofresearchgroups/invitrotoxicology/, and recently initiating his own group on Quantitative Genetic Toxicology. http://www.swansea.ac.uk/medicine/research/azofresearchgroups/genetictoxicologyquantitativeresearch/.

George Loizou, PhD

George Loizou is head of the Computational Toxicology Team within the Mathematical Sciences Unit of the Health and Safety Laboratory. He is a biochemical toxicologist with over 25 years' experience in quantitative, mechanistic chemical toxicology. He has been applying physiologically based pharmacokinetic (PBPK) modelling to analyse and explain toxicological data. The general aim of this work is to provide a quantitative basis to chemical risk assessment in support of the UK Health and Safety Executive and external customers. His work involves the development of user-friendly tools for quantitative, data-informed chemical risk assessment e.g., the rapid generation of PBPK models, the incorporation of human inter-individual variability into chemical risk assessment, interpretation of biological monitoring and the use of in vitro techniques to study the metabolism and mode of action of chemicals.

Prof. Amin Rostami-Hodjegan, PhD, FCP, FAAPS, FJSSX

Amin is a Professor of Systems Pharmacology at the Centre for Applied Pharmacokinetic Research (CAPKR) in the Pharmacy School at the University of Manchester. He has an active program of training PhD students in CAPKR in Systems Pharmacology and Pharmacokinetics and numerous students have graduated under his supervision from the University of Sheffield, where he was a Professor of Systems Pharmacology before joining the University of Manchester in 2009. As the Vice President of Research & Development at Simcyp Limited (a Certara Company), Amin leads a team of over 30 scientists working on extrapolation of in vitro data on drug metabolism to predict in vivo pharmacokinetics and pharmacodynamics in virtual patient populations. Professor Rostami has authored/co-authored over 150 peer-reviewed full articles and serves on the Editorial Boards of several journals. He has been an invited speaker at over 140 national and international meetings and has led a number of hands on workshops in the area of in vitro-in vivo extrapolation as applied to ADME in Drug Development.

Wout Slob, PhD

Dr. Wout Slob has a master degree in biology, and a PhD in mathematical biology. He has been associated with RIVM, the National Institute of Public Health and Environment in the Netherlands, since 1986. During the first years he worked as a general statistical consultant, but soon he specialized in the field of risk assessment. Between 2000 and 2010 he was associated with IRAS (Institute of Risk Assessment Sciences, which is part of the University of Utrecht) as a part time professor in quantitative risk assessment. His main fields of interest are dietary exposure modeling, dose-response modeling, and probabilistic risk assessment. He was involved in expert groups of many international organizations, including ILSI, JECFA, EFSA, IPCS and OECD. He developed the PROAST software package, a comprehensive tool for analyzing dose-response data and BMD calculations.

Lya Soeteman-Hernández, PhD

Lya Soeteman-Hernández is a genetic toxicologist at the National Institute for Public Health and the Environment (RIVM) in The Netherlands. She holds a PhD in Anatomy and Cell Biology/Toxicology from Queen's University in Canada. Dr. Soeteman-Hernández is an expert advisor in The Netherlands (VWS and NVWA) and internationally (ECHA, ILSI/HESI) for the assessment of the safety of chemicals. She has been involved in dose response modelling, applying it innovatively to genotoxicity data for cancer potency determination. Through this work, she collaborates closely with key government agencies (Health Canada, US Food and Drug Administration), academic institutions (Swansea University), and prominent international standard setters (ILSI/HESI). Dr. Soeteman- Hernández is an active member of the ILSI/HESI Genetic Toxicology Technical Committee (GTTC) where she performs the quantitative dose-response analysis using the benchmark dose approach to derivate point of departure estimates from genetic toxicology studies and advices on the potential of using quantitative genotoxicity data in cancer risk assessment.

Paul A. White, PhD

Paul White is currently a Canadian government research scientist, and adjunct professor of biology at the University of Ottawa. With respect to the former he is the Leader of the Genetic Toxicology Laboratory Group. With respect to the latter, he is a member of the Centre for Advanced Research in Environmental Genomics, the Ottawa-Carleton Institute of Biology, and the graduate program in Chemical and Environmental Toxicology. His research program focusses primarily on the sources, fate and hazards of mutagenic and carcinogenic contaminants; in particular those presented as complex mixtures in complex environmental matrices (e.g., urban air, vehicle exhaust, house dust, contaminated soils). His current work is also investigating the suitability of various in vitro and in vivo approaches for genetic toxicity assessment, regulatory decision-making, and risk assessment; moreover, the use of quantitative methods for the analysis of genetic toxicity dose-response data and the determination of genetic toxicity point-of-departure metrics for use in regulatory evaluations and decision-making.

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Xenometrix AG

Paul White
Health Canada

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National Institute of Health Sciences

*by webconference

2013–2014 Activities and Accomplishments

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Procter & Gamble Company

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Sanofi

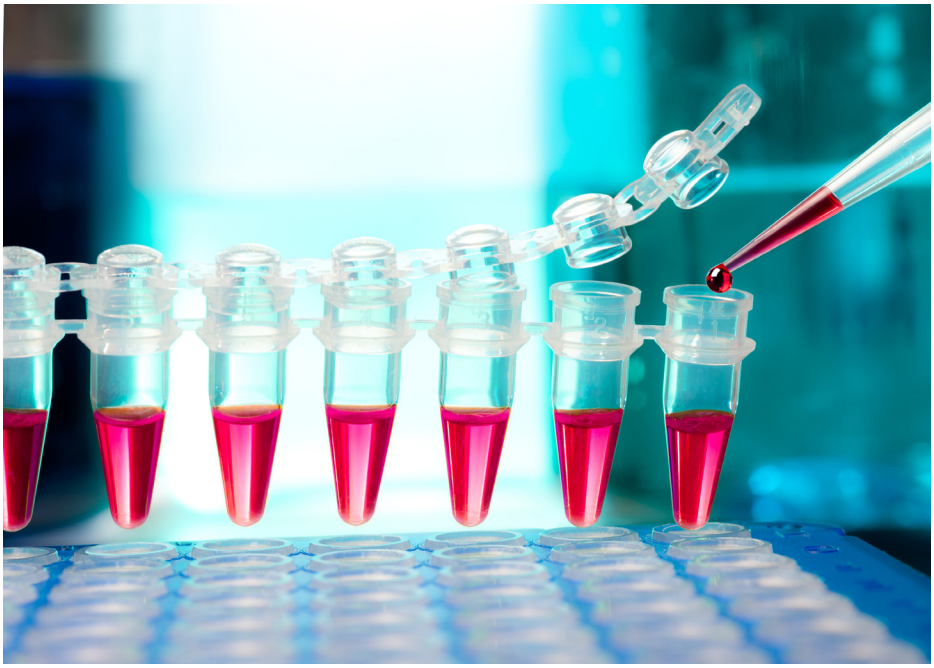
Dr. Jan van Benthem
National Institute for Public Health and the Environment (RIVM, The Netherlands)

HESI manager:

Dr. Jennifer Young Tanir

HESI associate:

Brianna Farr



This scientific program is committed to:

- Moving the field of genetic toxicology from a qualitative science to quantitative approaches to better understand human health risk, and promoting this "paradigm shift" of how genotoxicity data are used in risk assessment practices.

Areas of scientific focus:

- Improving the scientific basis of the interpretation of results from genetic toxicology tests for purposes of more accurate assessment of human risk.
- Developing follow-up strategies for determining the relevance of test results to human health.
- Providing a framework for integration of testing results into a risk-based assessment of the effects of chemical exposures on human health.
- Promoting the integration and use of new/emerging technologies and scientific knowledge in genetic toxicology hazard and risk assessment.
- Monitoring and promoting the development of innovative test and testing strategies.

Why get involved?

- Opportunity to interact with many international experts in the field of genetic toxicology.
- Integrate new technologies and scientific knowledge into genotoxicity evaluation and risk assessment.

Key accomplishments:

- Six new committee work groups developed workplans including detailed objectives, major milestones, and expected deliverables and made progress toward achieving their goals. The new work groups cover the topics of: (1) data interpretation, (2) new models in germ cells, (3) evaluation of new compounds: biologics, (4) evaluation of new compounds: nanomaterials, (5) framework for adoption of new test methods, and (6) "clean sheet" testing strategy.
- International outreach by the committee included a symposium at the International Congress of Toxicology (ICT) conference, a workshop at the Environmental Mutagenesis and Genomics Society (EMGS) annual meeting, and active participation and sponsorship of the Sixth International Workshop on Genotoxicity Testing (IWGT), as well as the International Conference on Environmental Mutagens (ICEM) and the Genetic Toxicology Association (GTA) annual meeting.
- Two publications were completed, including a second manuscript comparing statistical analysis methods of genotoxicity dose-response data compiled by the committee and a manuscript based on a 2012 workshop exploring how advances in knowledge and technologies outside of genetic toxicology might be applied and integrated.

The Committee's focus for May 2014–May 2015:

- *Workshop on Genetic Toxicology at the Crossroads: From Qualitative Hazard Evaluation to Quantitative Risk Assessment*. The committee will hold this satellite workshop following the European Environmental Mutagen Society 2014 Annual Meeting hosted by the UK Environmental Mutagen Society in Lancaster, United Kingdom, on 10–11 July 2014.
- *Quantitative Analysis*. The work group continues its collaboration with Health Canada to evaluate additional chemicals and assays for dose-response modeling. The application of these approaches to risk assessment and mode of action will also be explored.
- *Improving Existing Assays*. This work group was formed as a follow-up to the 2009 IWGT meeting and will sunset upon completion of three manuscripts on the topics of metabolism, cell comparison, and cell repository.
- *Data Interpretation*. This work group aims to provide guidance on interpretation of genotoxicity test outcomes, and is initially focused on the *in vitro* micronucleus assay acceptance and evaluation criteria.
- *New Models in Germ Cells*. The work group is focusing on developing an optimal protocol for conducting the transgenic assay in germ cells, performing a SWOT analysis of *in vivo* tests (in collaboration with IWGT), and developing a new and improved model for germ cell risk assessment.
- *Evaluation of New Compounds: Biologics*. This work group is focused on identifying specific challenges in genetic toxicology testing of biologics and providing recommendations for best-practice approaches.
- *Evaluation of New Compounds: Nanomaterials*. The work group is now evaluating the current testing paradigm for genotoxicity assessment of nanomaterials and modifying/influencing as needed.
- *Framework for Adoption of New Test Methods*. This work group is focused on evaluating the processes for validation of new test methods.
- *Pig-a Assay*. The work group is continuing to work on providing data for the validation of this assay as an *in vivo* gene mutation assay for safety assessments.
- *Clean Sheet Testing Strategy*. The goal of this work group is to develop a genetic toxicology testing strategy from a clean slate, incorporating new science and technology.

Recent publications:

Johnson GE, Soeteman-Hernández LG, Gollapudi BB, Bodger OG, Dearfield KL, Heflich RH, Hixon JG, Lovell DP, MacGregor JT, Pottenger LH, Thompson CM, Abraham L, Thybaud V, Tanir JY, Zeiger E, van Benthem J, White PA. (2014). Derivation of point of departure (PoD) estimates in genetic toxicology studies and their potential applications in risk assessment [published online ahead of print May 6, 2014]. *Environ Mol Mutagen*. doi:10.1002/em.21870.

Zeiger E, Gollapudi B, Aardema MJ, Auerbach S, Boverhof D,Custer L, Dedon P, Honma M, Ishida S, Kasinski AL, Kim JH, Manjanatha M, Marlowe J, Pfuhler S, Pogribny I, Slikker W, Stankowski LF Jr, Tanir JY, Tice R, van Benthem J, White P, Witt KL, Thybaud V. Genetic toxicology: opportunities to integrate new approaches. *Environ Mol Mutagen*. Submitted April 2014.

2013–2014 Participating organizations:

Aarhus University
Abbott Laboratories
AstraZeneca AB
Bayer HealthCare AG
BioReliance
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Celgene Corporation
Covance
ENVIRON
Errol Zeiger Consulting
Exponent
Federal Institute for Drugs and Medical Devices (BfArM, Germany)
GlaxoSmithKline
Health Canada
Hoffmann-La Roche Inc.
ILS-Inc.
Institut de Recherches Internationales SERVIER
Janssen Pharmaceuticals
Kirkland Consulting
Leiden University Medical Center
Litron Laboratories
L'Oréal Corporation
National Institute for Public Health and the Environment (RIVM, The Netherlands)
National Institute of Environmental Health Sciences
National Institute of Health Sciences (Japan)
New York Medical College
Novartis Pharma AG
Pfizer Inc.
Procter & Gamble Company
Sanofi
St. George's University of London
Swansea University
Takeda Pharmaceutical Company Limited
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US Environmental Protection Agency
US Food and Drug Administration

For more information, contact the Committee's manager, Dr. Jennifer Young Tanir, jtanir@hesiglobal.org.

INTERNATIONAL LIFE SCIENCES INSTITUTE (ILSI)

ANTITRUST STATEMENT

The Branches and Institutes of ILSI, including their respective Boards of Trustees, Scientific Advisors, Scientific Directors, Members, Committees, Subcommittees, Task Forces, and Working Groups, meet to promote understanding and resolution of significant health, nutrition, and safety issues that confront the public, industry, and government. With this goal in mind, ILSI meetings should be occasions where members' representatives and other invited participants:

1. Discuss scientific solutions to problems affecting the health, nutrition, and safety of the public.

2. Develop means to contribute to proper analysis of public health, nutrition, and safety issues by regulatory bodies.

3. Review industrial activities and problems with implications for public health, nutrition, and safety, and review new scientific developments.

4. Support and promote research and educational programs to enhance public health, nutrition, and safety.

5. Develop objective and voluntary industry standards to promote health and safety and compliance with regulatory requirements.

ILSI meetings shall not be occasions where members' representatives and other invited participants:

1. Discuss prices or pricing policies, or any marketing policy with a direct or indirect effect on pricing or any other terms of sale.

2. Confer about division or allocation of sales territories or customers.

3. Establish blacklists or boycotts of suppliers, purchasers, or competitors.

4. Coerce members to implement particular programs or policies.

5. Resolve problems unique to a single member or a small, select group of members.

6. Exchange or disseminate information relating to costs of production, distribution, or marketing.

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International Life Sciences Institute Code of Ethics and Organizational Standards of Conduct

Statement of Purpose

The goal of the International Life Sciences Institute's (ILSI) Code of Ethics and Organizational Standards of Conduct is to assure that ILSI members, scientific advisors, consultants, other key stakeholders in ILSI scientific activities, and users of ILSI's scientific work products are aware of the ethical principles guiding the organization's structure and the tenets behind the organization's adherence to rigorous, peer-reviewed scientific investigation and scientifically balanced, evidence-based work products. All scientists who work with ILSI shall be provided with a copy of this document.

Introduction

The International Life Sciences Institute is an international organization that seeks to promote [the] public health through the advancement of peer-reviewed scientific investigation and application of evidence-based decision-making in the areas of nutrition, food safety, toxicology, risk assessment, and the environment. ILSI accomplishes its mission through support of scientific research, publications, and workshops and conferences and other scientific activities. The principles listed below provide a framework to guide ethical decision-making. (Note: Reference below to policies applicable to "ILSI" includes ILSI, ILSI branches, and the ILSI Research Foundation.)

Principle 1. Scientific Integrity

All ILSI projects must have a primary public purpose and benefit, and must address issues of broad public health interest.

The ILSI, ILSI branches, and ILSI Research Foundation Boards of Trustees must be composed of at least 50 percent public sector members (primarily academic); the remaining trustees represent ILSI member companies. ILSI's trustees serve in a voluntary capacity; they are not paid for their time and are not personally eligible to receive grants from the ILSI entity on whose Board they sit.

ILSI shall only support animal and human subject research that has been approved by the appropriate bodies responsible for ensuring humane and ethical treatment of the animals or human subjects (e.g., Institutional Review Boards, Ethical Clearance Committees, Animal Care and Use Assurance Committee, etc.). All ILSI-supported research shall be conducted to meet the highest scientific standards as well as all applicable legal standards.

All ILSI sponsored research shall be conducted objectively and transparently so that the structure of the research is presented factually and without bias; be verifiable and reproducible.

ILSI encourages publication of all research results, regardless of outcome. ILSI entities shall not control the content of publications of research grantees or commissioned authors, but shall encourage academic freedom.

All ILSI research grantees must include language in their grant-related publications identifying the sponsor and providing appropriate sponsor contact information.

All ILSI committees and task forces must have scientific advisors from academia or government to ensure multi-sector input and balance, [and ILSI will only undertake activities for which there is broad interest and support.] All compensation (honoraria) provided to advisors must be disclosed by the advisors to the committee or task force overseeing the work.

Members of ILSI committees or task forces who are in attendance at meetings, symposia, or workshops must identify themselves on registration forms and materials by their primary affiliation (i.e., employer).

ILSI will be transparent in the disclosure of its funding sources.

Prinicple 2. Conflict/Declaration of Interest/Bias

ILSI believes that ensuring balance of perspectives is the most appropriate way to ensure that the impact of any potential conflict of interest or bias is minimized and does not exert an undue influence on the scientific process.

To this end, ILSI operates with transparency, conducts activities objectively, and is accountable to all stakeholders.

ILSI trustees must declare any potential bias or interest, including but not restricted to financial interests, and may be asked to recuse themselves from voting on issues that might be construed as conflicts of interest.

With respect to publications, grant reviews, and expert panels, ILSI expects the scientists with whom it works to [disclose] declare any potential [conflicts of] financial interest. ILSI may ask scientists to excuse themselves from an activity based on such a declaration.

Scientists who work with ILSI are expected to act in accordance with their own institution's conflict of interest policies and with applicable laws, as well as comply with the conflict of interest policies of any journal or organization with which they may work, including ILSI.

Principle 3. Advocacy

Advocacy of any kind is strictly limited to promotion of the use of evidence-based science as an aid in decision-making. ILSI does not conduct lobbying activities.

Principle 4. Transparency in Meetings and Publications

The purpose of and funding sources for all ILSI sponsored meetings, symposia, conferences, seminars, and workshops will be fully disclosed in meeting materials.

All invited presenters will provide declarations of financial interest to be disclosed if relevant at the time of the meeting (orally or in the meeting materials).

All ILSI publications must reflect the high standards of the organization. ILSI-sponsored manuscripts must undergo stringent peer-review by qualified reviewers. Editors and reviewers will treat manuscripts under review as confidential. Scientists are expected to recuse themselves as editors or reviewers of manuscripts if past or present connections with the author(s) preclude an objective evaluation of the work.

Authors of ILSI-sponsored publications shall make full, signed disclosures of financial and/or other interests (e.g., industry relationships, advisory relationships, or other conflicts of interest) that would reasonably appear to affect the contents of the article.

All ILSI publications, including proceedings from workshops or symposia sponsored by ILSI branches, the Research Foundation, or international committees will utilize appropriate attribution language to denote funding sources and sponsors, and ILSI entities shall provide contact information in all publications they produce for anyone interested in obtaining additional information about the organization or the specific sponsors of a particular project.