

Relevance and Follow-up of Positive Results in *In Vitro* Genetic Toxicity Tests (IVGT) : An ILSI-HESI Initiative

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GTA Fall Meeting, 10-11 September 2008



H E S I

Presentation Outline

- **What is ILSI-HESI?**
- **Background on the selection of IVGT project by HESI**
- **IVGT committee activities in 2006**
- **IVGT committee activities in 2007**
- **IVGT committee activities in 2008**

What is ILSI-HESI?

ILSI = International Life Sciences Institute

HESI = Health and Environmental Sciences Institute

MISSION STATEMENT: To stimulate and support scientific research and educational programs that contribute to the identification and resolution of health and environmental issues of concern to the public, scientific community, government agencies, and industry.

ILSI-HESI (contd.)

❖ Membership-based non-profit organization:

- ❖ Companies pay annual fees to be members
- ❖ Some project funding also comes from government and other sources

❖ Transparent:

- ❖ All work is published and publicly available

❖ Global scientific organization:

- ❖ High quality scientific papers, meetings, and research

ILSI-HESI (contd.)

- **Diverse:**
 - Academic advisors and government scientists are critical participants in projects and have significant input.
 - Tripartite approach is key: industry + academic + government scientists.
- **Responsive to a Broad Constituency:**
 - New research program ideas solicited from industry, academic and government scientists internationally
 - *Annual Emerging Issues process.*

What is ILSI-HESI?

HESI Membership

- ❖ Pharmaceutical Industry
- ❖ Agricultural Chemicals
- ❖ Chemical Industry
- ❖ Consumer Products
- ❖ Biotechnology Products
- ❖ Petrochemicals

***53 corporate members as of July 2007
(representing 10 countries on 3 continents)***

2008 HESI Scientific Portfolio

Technical Committees

- Application of genomics to mechanism-based risk assessment.
- Development and application of biomarkers of toxicity.
- Developmental and reproductive toxicology.
- Immunotoxicology.
- Integration of biomonitoring exposure data into the risk assessment process.
- Nonclinical/clinical safety correlations.
- Protein allergenicity.
- Risk assessment methodology.

Project Committees

- Biological significance of DNA adducts.
- Cancer hazard identification strategies.
- Development of methods for a tiered approach to assess bioaccumulation.
- CV safety – Proarrhythmia models.
- Nanomaterial environmental, health and safety.
- PPAR agonist tumorigenicity.
- Relevance and follow-up of positive results from *in vitro* genotoxicity assays.

Emerging Issues Subcommittees (* = Pending)

- Risk assessment for sensitive populations.
- Emergence of animal alternative needs in environmental risk assessment.
- State of the science: evaluating epigenetic changes.
- Short-term exposure to carcinogens. *
- Distinguishing adverse from non-adverse effects. *

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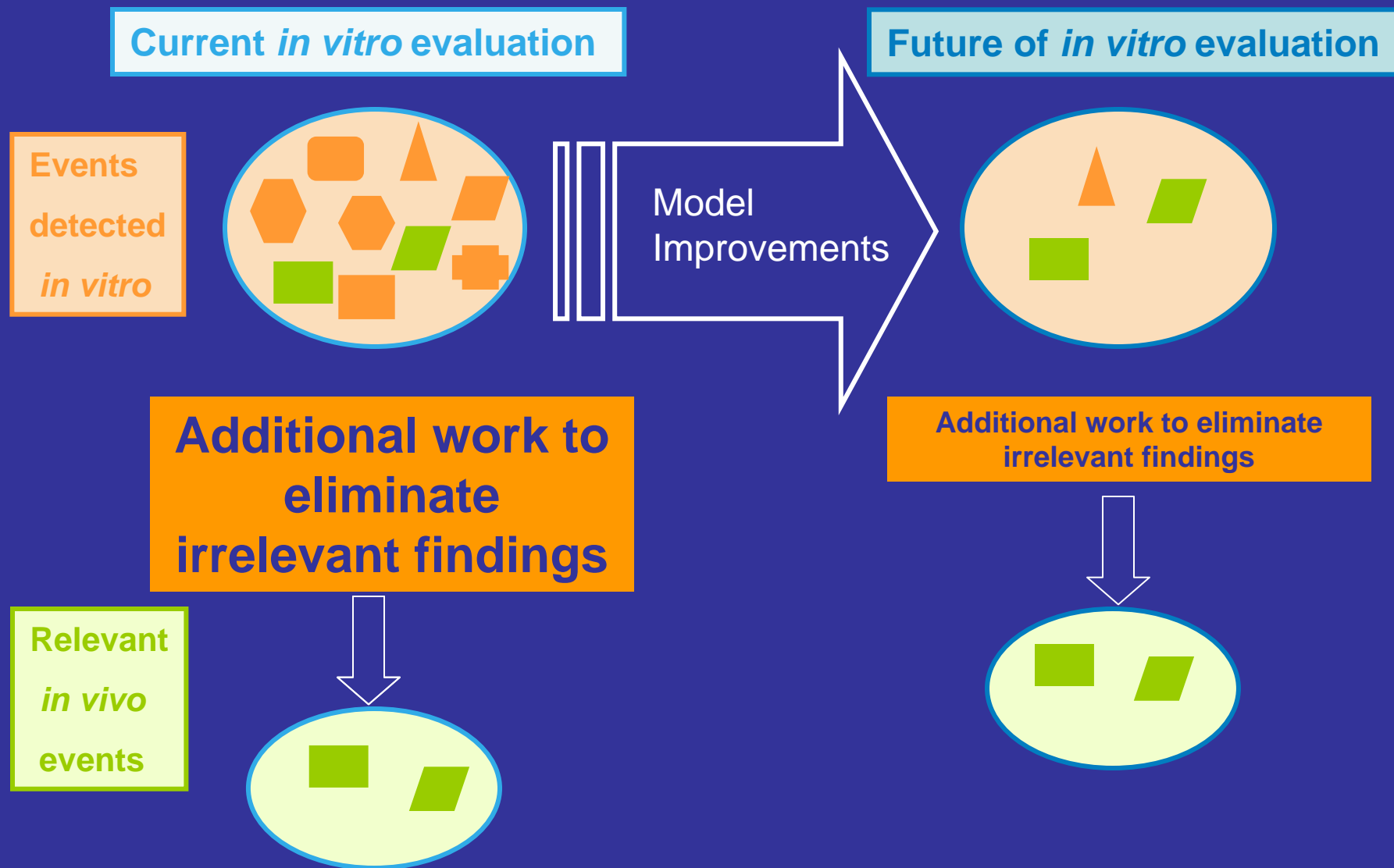
Context to HESI-IVGT Effort

- Relatively high rate of positive results in the *in vitro* tests
 - primarily in the mammalian cell assays
- Low specificity
 - many *in vitro* results, especially in the *in vitro* chromosome damage tests, not confirmed in the *in vivo* genetic toxicology tests and/or in carcinogenicity studies

Consequences

- De-selection of potentially useful compounds of low risk to humans
- Trigger numerous additional studies, including *in vivo* and mechanistic studies, to further evaluate the level of concern and risk for humans

Opportunity for improvement



HESI-IVGT Objectives

1. To improve the scientific basis of the interpretation of results from *in vitro* genetic toxicology tests for purposes of accurate human risk assessment.
2. To develop follow-up strategies for determining the relevance of *in vitro* test results to human health.
3. To provide a framework for the integration of the *in vitro* testing results into a risk-based assessment of the effects of chemical exposures to human health.

IVGT Steering Team

- **Dr. Marilyn Aardema**,
The Procter & Gamble Company, USA
- **Dr. Daniel Casciano**
(formerly) US FDA NCTR
- **Dr. Vicki Dellarco**
US EPA, Office of Pesticide Programs
- **Dr. Michelle Embry (HESI staff)**
ILSI-HESI, USA
- **Dr. B. Bhaskar Gollapudi (Vice-chair)**
The Dow Chemical Company, USA
- **Dr. Masa Honma**
Nat'l Institute of Health Sciences,
Japan
- **Dr. James Kim**
ILSI-HESI, USA
- **Dr. David Jacobson-Kram**
US FDA
- **Dr. Peter Kasper**
BfArM, Germany
- **Dr. James MacGregor (scientific advisor)**
Toxicology Consulting Services,
USA
- **Dr. Robert Rees**
GlaxoSmithKline, United Kingdom
- **Dr. Veronique Thybaud (Chair)**
sanofi-aventis, France

Industry Membership of the Committee

❖ Currently have 19 industry members (~25 scientists)

- Amgen
- AstraZeneca
- BASF
- Bayer Healthcare Pharma
- Bristol-Meyers Squibb
- Coca-Cola
- The Dow Chemical Co.
- GlaxoSmithKline
- Johnson & Johnson
- L'Oreal
- Merck
- Mitsubishi
- Novartis
- Pfizer
- Procter & Gamble
- sanofi-aventis
- Schering Plough
- Servier
- Takeda

Contribution of scientists from regulatory and academic institutes

- 7 regulatory agencies represented (~12 scientists)
- 3 Scientists from University
- 2 consultants

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June 2006 International Workshop

- 45 experts from the U.S., Canada, Europe, and Japan
- Participants asked to address 3 major questions:
 1. How to establish relevance of *in vitro* findings to humans using mechanistic and *in vivo* data?
 2. How to factor in a quantitative consideration of the impact of dose response?
 3. How to improve testing for genetic toxicity?

1: How to establish relevance of *in vitro* findings to humans using mechanistic and *in vivo* data

- Re-evaluate 10 mM upper limit using a retrospective analysis:
- Apply general weight of evidence principles of data interpretation accepted for other types of toxicity :
- Examine the suitability of applying the concepts of benchmark dose, NOAELs, LOAELs, and uncertainty factors to genotoxicity data.
- Conduct a retrospective in-depth review of genotoxicity databases to understand the contribution of *in vitro* and *in vivo* assays to the prediction of carcinogenic potential.

2: How to factor in a quantitative consideration of the impact of dose response?

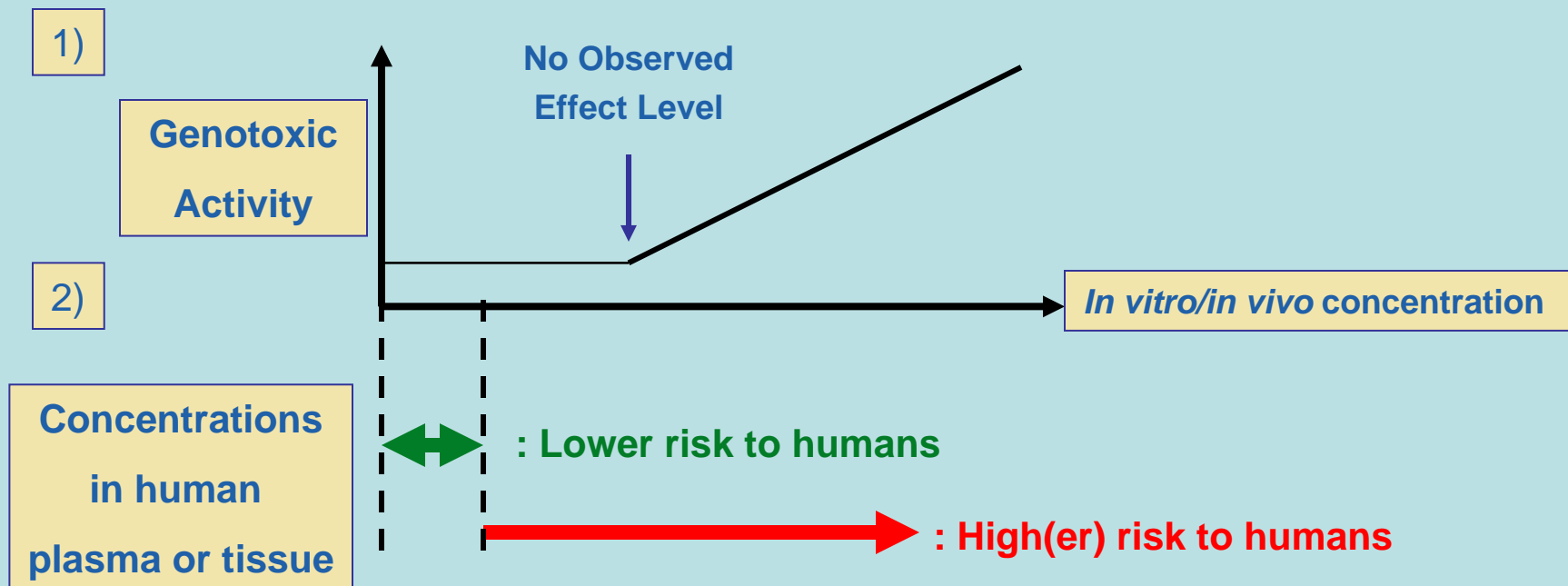
- Determine feasibility of a tiered or quantitative classification system for genotoxic hazard
- Evaluate databases to determine scientific support for low dose linearity *versus* practical thresholds for different classes of genetic toxicants.
- Use *in vivo* dose–response and human exposure information in a weight of the evidence approach to evaluate human risk.
- Define the limitations of *in vivo* methods to facilitate effective use of the test data.

3: How to improve genetic toxicity testing?

- **General agreement that new tests and approaches are needed.**
- **Parallel multi-stakeholder activities are recommended to make progress in a reasonable time frame.**

From qualitative to quantitative evaluation

- 1) Determination of NOEL concentration/dose
- 2) Comparison to human exposure



2006 Workshop outcome

❖ Publication:



Available online at www.sciencedirect.com



Mutation Research 633 (2007) 67–79

www.elsevier.com/locate/gentox

Community address: www.elsevier.com/locate/mutres

Current issues

Relevance and follow-up of positive results in *in vitro* genetic toxicity assays: An ILSI-HESI initiative[☆]

Véronique Thybaud^a, Marilyn Aardema^b, Daniel Casciano^c, Vicki Dellarco^d,
Michelle R. Embry^{e,*}, B. Bhaskar Gollapudi^f, Makoto Hayashi^g, Michael P. Holsapple^e,
David Jacobson-Kram^h, Peter Kasperⁱ, James T. MacGregor^j, Robert Rees^k

❖ Recommendations for follow-up

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Follow-up Activities

- Organized a second workshop in June of 2007
- Identified two primary initiatives:
 - Examination of emerging technologies and new strategies
 - Development of a decision tree for follow-up strategies in case of positive findings

EMERGING TECHNOLOGIES / NEW STRATEGIES

- Hold a workshop on emerging technologies focusing on:
 - screening tests
 - replacements for initial tests (long-term)
 - follow-up tests (piggy back on standard toxicity tests)
- Coordinate a “ring-trial” of new technologies using a set of model chemicals

DEVELOPMENT OF A DECISION TREE FOR FOLLOW-UP STRATEGIES

- One team (Review Group, lead by Veronique Thybaud) is tasked with:
 - evaluating the existing strategies
 - development of a decision tree
 - identification of needed improvements to the existing assays and the missing ones to aid in the decision process.
- A second team (Quantitative Group, lead by Bhaskar Gollapudi) is tasked with:
 - developing quantitative information to support the decision tree
 - *in vitro* to *in vivo* comparison and extrapolation
 - *in vivo* rodent to human comparison and extrapolation
 - threshold evaluation

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2008 Activities

- Organized an International Workshop on Novel and Emerging Technologies in Genetic Toxicology in May
 - Proceedings to be published in Environmental and Molecular Mutagenesis
- Various teams are busy working on their respective breakthrough initiatives.

*..... moving genetic toxicology forward from
purely a hazard identification
science to better informing the
human risk*

Thank You!

Recommendations for Follow-up:

Q1: How to establish relevance of *in vitro* findings to humans using mechanistic and *in vivo* data

- Re-evaluate 10 mM upper limit using a retrospective analysis:
 - animal and human pharmacokinetic data
 - metabolic efficiency and enzyme saturation
 - typical blood and tissue levels at the most extreme human exposure
- Apply general weight of evidence principles of data interpretation accepted for other types of toxicity :
 - metabolism and kinetics
 - mechanism
 - dose–response and human exposure placing emphasis on reliable *in vivo* results over *in vitro* findings;
 - acknowledging data limitations
- Examine the suitability of applying the concepts of benchmark dose, NOAELs, LOAELs, and uncertainty factors to genotoxicity data.
- Conduct a retrospective in-depth review of genotoxicity databases to understand the contribution of *in vitro* and *in vivo* assays to the prediction of carcinogenic potential.

Q2: How to factor in a quantitative consideration of the impact of dose response?

- Determine the feasibility of developing a tiered or quantitative classification system for genotoxic hazard
 - examine relationship between *in vitro* and *in vivo* responses for different mechanistic classes,
 - correlate tissue exposure with genetic damage *in vivo* (including tumor response) and *in vitro*,
 - develop different bins of concern (e.g., low, intermediate, high) based on human exposure, *in vivo* potency (e.g., tumor data, genetic toxicity data) and *in vitro* concentration in relation to achievable *in vivo* exposure.
- Evaluate databases to determine scientific support for low dose linearity *versus* practical thresholds for different classes of genetic toxicants.
- Use *in vivo* dose–response and human exposure information in a weight of the evidence approach to evaluate human risk.
- Define the limitations of *in vivo* methods to facilitate effective use of the test data.

IVGT Committee History

- **Proposed as a topic of interest during the emerging issues process in Summer, 2004**
- **Prioritized by the EI Steering Committee in Fall, 2004**
- **Presented during the HESI Annual Meeting in Jan., 2005**
- **Added to the HESI portfolio in March, 2005**
- **Of 20 topics considered by HESI over the last 4 years, IVGT was the highest rated**
- **Steering team first met February, 2006**
- **First International Workshop held June 21-22, 2006**
- **Second International Workshop held June 5-6, 2007**