Application of Genomics for Health and Environmental Safety of Chemicals

Chemical Industry Perspective

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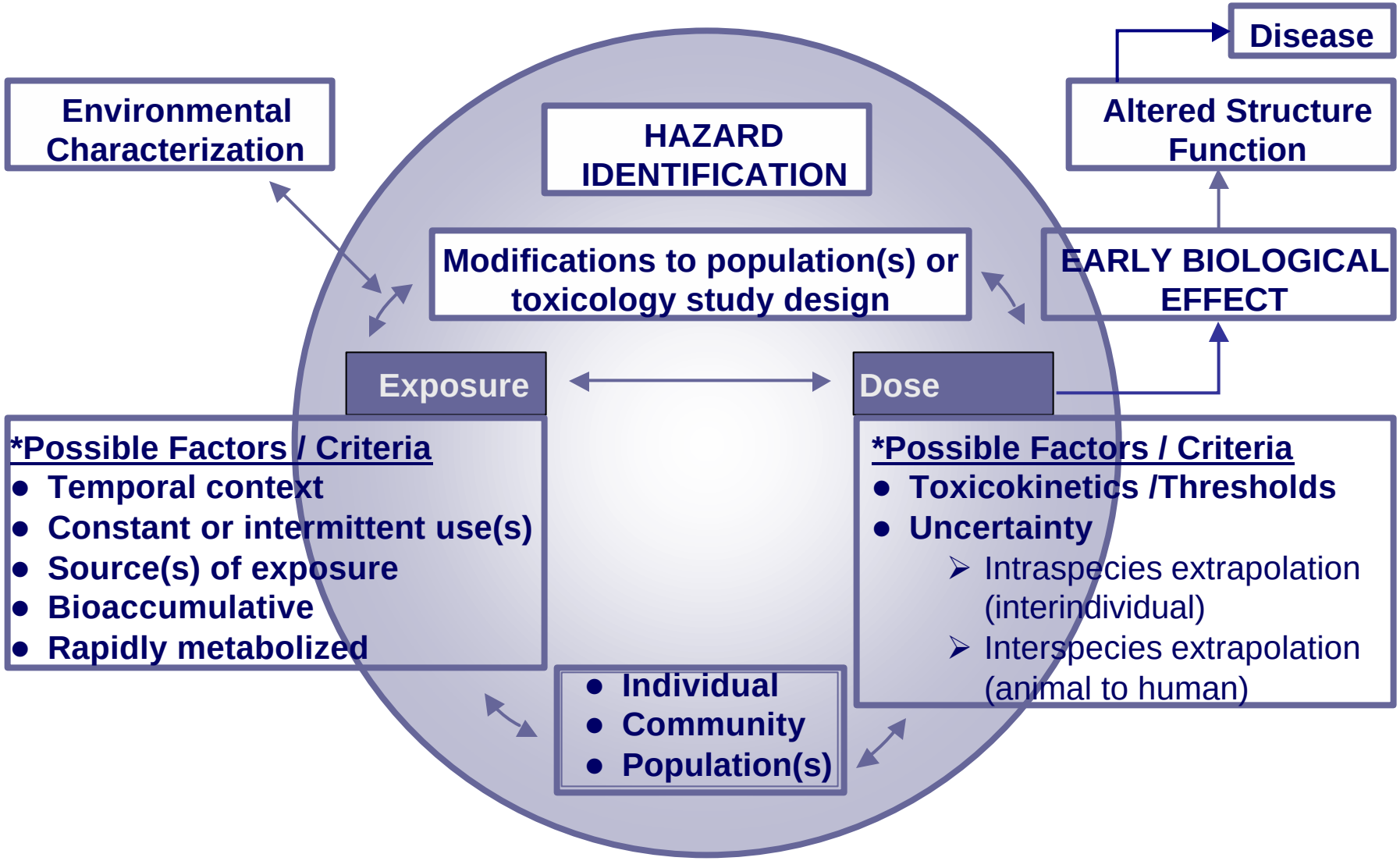
ASU - Workshop on Genetics and Environmental Regulations

The Promise of Genomics And Its Benefits to Chemical Safety

- **Opportunities for screening / priority setting**
- **Identification of biomarkers of chemical exposure, interaction and effect**
- **Improved understanding of mechanisms of action**
- **Improved understanding of the use and limitations of toxicological models**
- **Application for use in predictive toxicology models and risk assessment**
- **Identification and quantification of susceptible subpopulations**

Environmental Public Health Continuum*



*From ILSI-HESI Biomonitoring Workshop

Findings of 2002 International Multistakeholder Workshop[1]

- **"Omics" has great value and potential for improving toxicology, epidemiology, risk assessment, and the protection of human health and the environment**
  - **Technology should be validated and applied according to principles of established sciences such as toxicology**

- **Unified research agenda is urgently needed**

[1]*Environmental Health Perspectives, 2002 Oct. 110(10):1047-50*

Application of "Toxicogenomics" Understanding Mechanism (or Mode) of Toxicant Action

Identify key gene expression changes responsible for or associated with toxicity

Mechanistic Toxicology

←

Observed Toxicity

- **Benefit**
  - **Understanding of dose-response and thresholds**
  - **Interspecies extrapolation for risk assessment**

- **Challenges**
  - **Agreeing on statistically / biologically significant level of change**
  - **Changes occur along a continuum from inconsequential through adaptive to toxic**

Application of "Toxicogenomics"
Use of a "Molecular Signature" to Predict Toxicity

Change in gene expression pattern for a new chemical compared to patterns for known toxicants

Mechanistic Toxicology →

Predicted Toxicity

- **Benefit**
  - **Mechanistically based predictions**
  - **Faster, less expensive, require fewer or no animals**

- **Challenges**
  - **Strength of the association for prediction**
  - **Potential to use prematurely**

Issues and Challenges

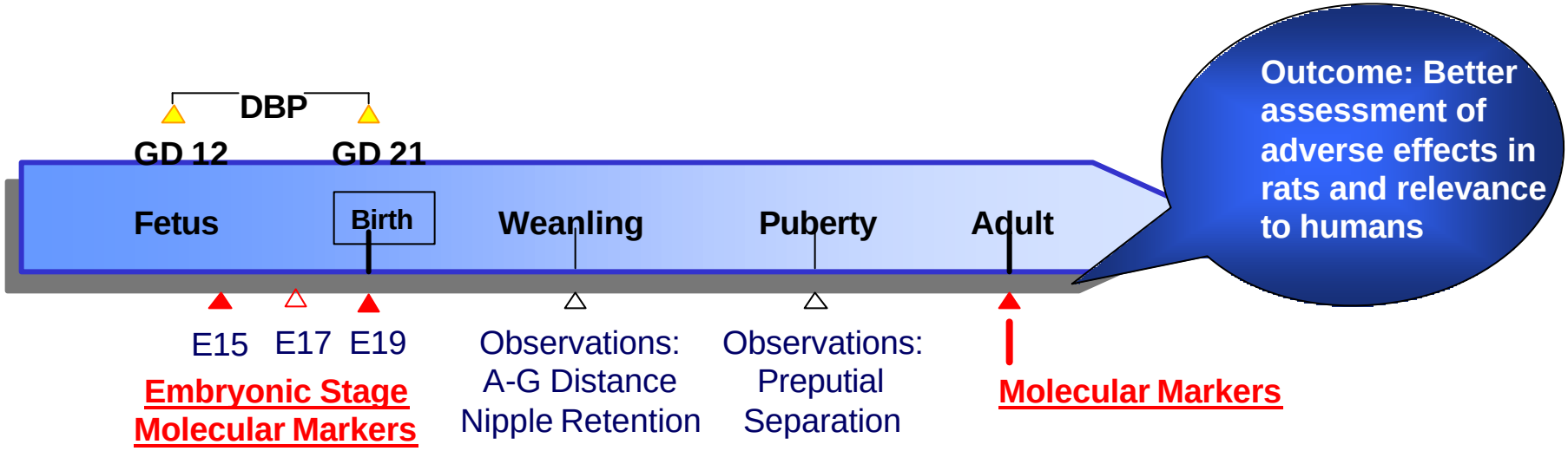
- **Technological**
  - **Validation of available technologies**
  - **Data comparison across multiple technologies**
  - **Different study designs and analytical methods**

- **Bioinformatics**
  - **Large volume of data**
  - **Validity of analysis methods**
  - **Consistency in data reporting**

Example of Application of Genomic Approach to Investigate Receptor-Mediated Reproductive Toxicity

- **Driven by need to understand relevance of reproductive toxicity in rodents to human risk assessment (e.g., phthalate high dose effects)**

- **Two program objectives:**
  - **Investigate the interaction of dibutyl phthalate (as a model) and appropriate metabolites with selected genetically engineered rat receptors and ability to activate bound nuclear receptor**
  - **Perform transcriptomics / bioinformatics on endocrine-active tissues (e.g. testes) after treatment of rats with DBP**
    - **Identify gene clusters and signaling pathways affected by binding of phthalates to nuclear receptors**



Preliminary Findings from Receptor-Mediated Reproductive Toxicity Study

- **Regulation of three functionally distinct gene clusters were down regulated in fetal testes of rats exposed to DBP *in utero* (500 mg / kg)**
  - **Synthesis of testosterone**
  - **Insulin-like factor 3**
  - **Protection against oxidative stress**

- **The effect on genes related to testosterone synthesis appeared to involve "leydig cells" but not "sertoli cells"**

- **DBP-induced changes on gene expression occurring during testes development were not propagated into adulthood**

- **Phenotypically, 65% of DBP-exposed fetuses (500 mg / kg) resulted in either bilateral or unilateral cryptorchidism and 70% reduction in fetal testes (GD19) testosterone levels**

Application of Findings and Next Steps

- **Provides insight to signaling pathways affected at the molecular level to high doses of DBP in rats**

- **Next steps:**
  - **Investigate the cellular specificity of the effect (Leydig vs. Sertoli cells)**
  - **Extend the response from *in vivo* to *in vitro* environment**
  - **Define the dose-response and threshold levels**

Example of Analysis of Genetic Differences in Risk Assessment

- **Project goal:**
  - **To develop a method that enables risk assessors to use genetic information for populations reliably in chemical risk assessments**
  - **To identify instances where traditional "uncertainty factor" approach can be replaced by more data-driven methods**

- **Approach**
  - **Identified polymorphisms in genes that code for metabolizing enzymes**
  - **Reviewed two substances, warfarin and parathion, that are known to be metabolized by these enzymes**
  - **Used statistical techniques to evaluate the extent to which polymorphism affected the internal dose for individuals and the population as a whole**

- **Results . . . Polymorphisms were**
  - **Warfarin -- A significant factor on variability in internal dose**
  - **Parathion - A minor contribution to internal dose variability**

*Gentry, R.R. et al. Tox Sci 70:120-139 (2002) - Funded by American Chemistry Council-Long-Range Research Initiatives

Example of Analysis of Genetic Differences in Risk Assessment (cont'd)

- **Demonstrated that data on polymorphisms can be combined with other knowledge to improve accuracy of human variability in risk assessment**
- **Identified the data needs for supporting such analyses and confirmed the utility of probabilistic application of PBPK modeling in determining narratives in population sensitivity for metabolism**
- **Application of these techniques enable risk assessors to use polymorphism data to more accurately predict tissue dose for populations**

Summary

- **Application of genomics to chemical management has significant promise**
- **Further research is needed for methods development, data collection and evaluation to understand how and when to apply these technologies**
- **Genomics can help in better understanding population genetic variability and reduce uncertainty in chemical risk assessments**